GENETIC DISORDERS ON THE ISLAND OF MAURITIUS

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for the degree of Doctor of Medicine

Colin E. Wallis MB., ChB.

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The Island of Mauritius, from the Atlas of Pierre van der Aa, 1721.

DECLARATION

I, Colin E. Wallis, hereby declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

This thesis is for the disabled children of Mauritius and is dedicated to their families.

ABSTRACT

Genetic disorders on the Island of Mauritius

Inherited disorders are an important cause of physical handicap, deafness, mental retardation and blindness. There is considerable variation in the geographic and ethnic distribution of genetic disease due to biological pressures and historical accidents. In this context the relative prevalence of common inherited disorders and the recognition of rare conditions in isolated communities is of great academic importance.

Oceanic islands are of special significance in the study of inherited disease. Virtually nothing has been documented concerning genetic disorders on the Island of Mauritius with a population of one million people. This study was undertaken to document the impact of inherited disorders on handicapping conditions in this community.

As genetic disease concentrates in institutions, formal screening of all the schools for the deaf and blind, and the associations for the physically and mentally handicapped on Mauritius was undertaken. This involved a careful history, clinical examination and genealogical study, with radiographic, biochemical and ancillary testing performed where appropriate. Referral clinics were also established for the assessment of individuals and families known, or thought to be afflicted with abnormalities or handicap of a genetic origin. To ensure completeness, a similar survey was performed on Rodrigues, a neighbouring island, as this community is included under the responsibilities of the Mauritian Ministry of Health.

Accumulated data concerning 681 patients were analysed. Genetic disorders accounted for disability in 265 individuals representing 38,6% of the causes of handicap. Of these persons 54 were deaf, 30 were blind, 99 were mentally retarded and 80 were physically handicapped.

Several new entities, considered unique to the area and a consequence of either consanguinity or the founder effect, were documented. Karyotyping on selected individuals was undertaken in the laboratories of the Department of Human Genetics, University of Cape Town. A molecular genetic study of a large family with X-linked deafness of Nance, conducted by the same laboratory, revealed tight linkage with the probe pDP34; linkage analysis was performed on patients with Duchenne muscular dystrophy.

The collation of these original data, the delineation of the new genetic conditions and an analysis of the results form the subject of this thesis and provide a basis for the future development of genetic services on Mauritius.

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All the clinical photographs, unless otherwise indicated, were taken by the author with the subjects' permission. The Trustees of the British Library are thanked for the Frontispiece and Figure 3.3.

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FORMAT AND ABBREVIATIONS

AD = autosomal dominant

AR = autosomal recessive

XL = X-linked recessive

McK = McKusick catalogue number (McKusick, 1986)

km = kilometres

m = metres

? = unknown or unestablished

N = normal

MH = mental handicap

PH = physical handicap

 = affected male

 = unaffected male

 = affected female

 = unaffected female

 = deceased

Fig. = figure or illustration

Single spaced italic print has been used for selected case reports in order to reduce the bulk of the text. Figures and tables are incorporated within the text of the thesis and positioned as proximal to the relevant script as layout would permit. All references are listed alphabetically in Section IX.

SECTION I

THE PROJECT

In this section, the background to the development of the project is presented and the aims and methodology are discussed.

Chapter 1: The Geographical Distribution of Genetic Disease.

Chapter 2: Aims and Methodology of the Survey.

CHAPTER ONE

THE GEOGRAPHICAL DISTRIBUTION OF GENETIC DISEASE

1.1 INTRODUCTION

There is considerable variation in the geographic and ethnic distribution of genetic diseases. The factors that influence the presence and prevalence of conditions in a particular community are often complex and intertwined. Historical accidents, biological pressures, the founder effect and inbreeding may each contribute to a unique disease profile for any specific population group.

Mechanisms which influence genetic isolation include the geographical barriers of mountains, rivers and oceans and the restrictions imposed by language, marital mores, religion or economic circumstances. Indeed, few communities can be regarded as homogeneous social entities as boundaries to breeding exist at many levels (Roberts, 1975).

In isolated communities the relative prevalence of genetic diseases and the recognition of rare or even unique conditions is of considerable academic and practical significance. An isolate is especially vulnerable to founder effects and the consequences of inbreeding; from this setting, new or unusual genetic entities may emanate. Examples include the delineation of AR cartilage-hair hypoplasia in the Amish of North America (McKusick et al, 1965) or the syndromic status of sclerosteosis in the Afrikaners of South Africa (Beighton et al, 1984).

Inherited disorders are an important cause of physical and mental handicap and may contribute significantly to the morbidity and mortality of a population. Many centres produce statistics concerning local congenital diseases, such as the catalogue of phenotypes found in the Netherlands (ten Kate, 1986) or the Australian Congenital Malformations Monitoring Report (1987). The practical benefits emerging from a documentation of genetic disease within a community include the implementation of effective genetic services and the planning of appropriate preventative and rehabilitation measures.

1.2 OCEANIC ISLANDS

The isolation of the inhabitants of an oceanic island offers a unique opportunity for medical research (Roberts and Beighton, 1986). The geographical area of study is clearly defined by the coastline and the population is confined by the sea. Massive immigration is rare, although there may be some emigration from the restrictive environment by those who are physically and intellectually capable of moving to a new country.

The founder effect could be responsible for the high prevalence on an island of a condition which is rare or absent in other parts of the world. This mechanism may occur when an unusual gene is present in a fertile member of the island's founding group. The limitations to large scale immigration prevent a dilutional effect of these high initial frequencies. Equally, the new dominant mutation of a gene for a handicapping condition such as St. Helena familial genu valgum (Beighton et al, 1986), might impair an individual's ability to leave the island. The departure of unaffected persons would further increase the prevalence of the disorder in the residual community.

Many island populations show a high frequency of rare autosomal recessive disorders, for example, Werdnig-Hoffmann disease on the Island of Réunion (Pascalet-Guidon et al, 1984). No two islands are likely to have the same spectrum of AR disease and, indeed, the community may be further sub-divided into smaller isolates, each with their own

characteristic conditions. Fraser (1963) noted that in three small villages on the Island of Krk in the Adriatic, each had its own distinct form of recessive disease, namely dwarfism, albinism and spastic paraplegia. AR blindness among the Pingolapese people of the Eastern Caroline Islands (Brody et al, 1970) is a further example.

A valuable aspect to a study of oceanic islands is the availability of documents that relate to significant and influential historical events (Shine, 1970). These milestones, be they cyclones, malaria or invasion by hostile forces, may cause sudden changes in the population size with a "bottle neck" effect that can considerably alter the existing genetic profile.

1.3 MAURITIUS - AN ISLAND FOR STUDY

The Island of Mauritius has much to offer an investigator of genetic diseases. Isolation by the Indian Ocean left the land uninhabited until the 17th century. Today the population has reached one million.

Geographically, Mauritius is situated at the crossroads of three civilisations - Africa, Europe and the East and this position is reflected in the diversity of its populace. During the Island's short history, disparate breeding groups have developed, separated by the cultural and social barriers of their origins. This situation provides an ideal setting for an academic appraisal of the effects of isolating mechanisms on the prevalence of inherited disorders in this island community.

The opportunities for an investigation of this nature are dwindling. Modern transportation, satellite communications and industrialisation are rapidly exposing many previously isolated areas. Geographical features no longer remain a barrier to modern day travel; cross-cultural communication and marriage is commonly encountered. For an island like Mauritius, the era of seclusion is over and the important genetic manifestations of isolation might soon be lost.

No previous survey into the inherited disorders on Mauritius has been undertaken but the introduction of an effective health care programme has now provided an infrastructure upon which such an investigation can be based. Institutions for the deaf, blind, mentally handicapped and physically disabled have been established and local medical care is readily available to the Island's inhabitants. There is, however, little knowledge of the contribution of genetic disease to morbidity and mortality. Entities that are significant by virtue of their increased prevalence, their rarity or their absence are undocumented. Unique disorders require delineation.

As the health care on Mauritius continues to develop, the implementation of a genetic service for the Island is inevitable. For this reason, a survey of inherited disorders would, in addition to the academic value, have practical benefit in the establishment of such a programme.

1.4 INHERITED DISORDERS IN A DEVELOPING COMMUNITY

The efficiency of primary health care programmes, with their introduction of preventative measures such as oral rehydration programmes and immunisation has resulted in rapidly changing morbidity and mortality patterns in many developing countries. For example, following the intervention of basic health care in rural areas of India, Kumar and Datta (1984) report an 8% relative increase in infant mortality from congenital malformations.

An analysis of data from India indicates a frequency of inherited diseases in that country which equates to the frequency in developed nations (Verma 1986). The realistic contribution of genetic disorders to mortality in the developing world often goes unrecognized due to the superimposition of infective or nutritional disease or the misdiagnosis of the inherited condition through a lack of diagnostic facilities or specialist expertise.

It might be argued that genetic services are of little importance in developing communities and that resources should be apportioned to more immediate health needs. This argument bears even greater relevance when considering the new and costly cytogenetic and molecular technologies which are emerging as essential tools for the study and practice of medical genetics. A potential solution to this problem lies not in establishing the technology within the developing community itself, but in the transportation of biological material to an established centre equipped with the

appropriate laboratory facilities. The logistics and feasibility of such a proposal have yet to be assessed and a study on Mauritius could explore these possibilities.

CHAPTER TWO

AIMS AND METHODOLOGY

2.1 AIMS

The study had the following initial aims:-

1) to identify the presence of genetic disease in the population of the Island of Mauritius with a special emphasis on the contribution of inherited disorders to handicapping conditions;
2) to collate and document this original data;
3) to delineate new genetic conditions; and
4) to establish protocols for the transport of biological material for cytogenetic and molecular study at suitably equipped laboratories.

The successful documentation of this information would provide a basis for the future development of a genetic service on the Island of Mauritius.

2.2 STUDY METHODS

The project consisted of three phases.

2.2.1 Phase I: PLANNING

Contact with the health authorities on Mauritius was established and an enthusiastic response to the aims and principles of the survey was received. Medical personnel on the Island were then advised of the scope of the study and communication was established with the heads of institutions that catered for handicapped individuals and with other interested organisations. Arrangements were made for the provision of an office, secretarial assistance and a motor vehicle to be available on the Island. Plans were made with the Department of Human Genetics, University of Cape Town, for use of their molecular and cytogenetic services and from the Blood Transfusion Service, Natal, for access to their laboratory facilities.

The main thrust of this project was the documentation of the impact of genetic disorders on deafness, blindness, mental handicap and physical disability on Mauritius. The haematological diseases, psychiatric disorders, inherited metabolic conditions and entities with multifactorial inheritance . were excluded from the study. The reasons for these constraints included a lack of local investigatory facilities, logistical problems in acquiring diagnostic laboratory data from overseas and limitations in the investigator's own expertise in certain fields.

2.2.2 Phase II: THE SURVEY ON THE ISLAND

During a three month period (March-May, 1987) the investigator resided on the Island and personally examined and documented individuals and families with possible genetic disease. The results of a medical history and physical examination were recorded on a pre-designed proforma (Appendix A) and photographs were obtained of interesting, unusual and illustrative features. Genetic counselling was given where appropriate.

Further details concerning the ascertainment and examination of individuals with inherited handicapping disorders are provided in the appropriate sections of this thesis. Essentially, data accumulation was from two main sources: institutional screening and individual patient referral. Home visits were made if further family members required examination or when affected persons were unable to travel to the clinic.

Local ancillary testing included radiographic studies and baseline biochemical investigations. Candidates for chromosomal analysis, skin biopsy and biomolecular investigations were carefully selected and this biological material was transported to the appropriate laboratories as described in Appendix B.

During phase II, several educational lectures were delivered to local health care personnel on medical aspects of human genetics and interviews with the media were given (Appendix D). These talks elicited goodwill, an understanding of the project and resulted in the referral of a number of interesting cases.

2.2.3 Phase III: DATA ANALYSIS

The accumulated patient data was entered into the computerised data-base programme (Dbase-III Plus) of the Department of Human Genetics, at the University of Cape Town. This procedure greatly facilitated analysis of information and simplified the recall of patient details.

During the survey, a number of patients were encountered in whom it was impossible to make a diagnosis. In some instances this reflected lack of access to the literature or relevant texts, but it was possible that certain individuals represented hitherto undelineated disorders.

This problem was approached in a number of ways. International authorities in specialised fields were contacted and supplied with the individual's history, clinical findings and ancillary data, including relevant photographs. The response was often rewarding and a number of rare genetic syndromes were diagnosed in this way.

A programme for the microcomputer-assisted diagnosis of inherited skeletal disorders was utilised to establish a differential diagnosis for certain bone dysplasias. The Birth Defects Information Service (Micro BDIS) of the Institute for Biomedical Communication at the South African Medical Research Council was accessed. Literature surveys of specified topics were undertaken through the Medline database system of the Institute for Biomedical Communication, MRC, Cape Town.

An important aspect of Phase III was the co-ordination of the laboratory investigations and collation of the biomolecular and cytogenetic findings. The results and consequences of these tests were communicated to the relevant physicians on Mauritius. At this juncture, certain studies demanded additional specimens from unsampled relatives in order to clarify provisional results and the acquisition of this material was arranged. Information regarding individual diagnoses was given to parents and referring physicians where indicated and a report on the survey was submitted to the Mauritian Ministry of Health.

The government of Mauritius is reponsible for a smaller inhabited island, **Rodrigues**, whose health care falls under Mauritian jurisdiction. For this reason, an extention of the survey involved an investigation into genetic disease on this second Island. The methods and results are described seperately in Section VII but, because of the administrative links to the Island of Mauritius, it was appropriate to include the findings for Rodrigues in the final analysis of this study (Section VIII).

SECTION II

L'ILE MAURICE

The prevalence of genetic disorders in any population group is significantly influenced by geographical constraints, historical events and natural disasters. To facilitate an understanding of the presence, prevalence and implications of inherited conditions on the Island of Mauritius, a brief account of the history, geography and demography of the Island is presented in this section.

Chapter 3: Geographical and Historical Considerations.

Chapter 4: Demography, Population and Culture.

CHAPTER THREE

GEOGRAPHICAL AND HISTORICAL CONSIDERATIONS

3.1 THE GEOGRAPHY OF MAURITIUS

Mauritius is an Indian Ocean island situated between the latitudes of 19° 58' and 20° 32' South (just inside the tropics) and meridians 57° 18' and 57° 48'East. The pear-shaped surface area of 1,850 square kilometres is just over half that of Greater London and almost equal to the Cape Peninsula. A distance of 47 kilometres seperates Flic en Flac (West) and Pointe Quatre Cocos (East) and the Island measures 61 kilometres from North to South (Fig. 3-I).

The land is volcanic in origin, and forms part of the Mascarenes, a group of islands comprising Réunion, Mauritius and Rodrigues (Fig. 3-2). Rodrigues is situated 320 nautical miles to the East of Mauritius. Although geographically isolated, this island is a political province of Mauritius. This thesis thus includes a section on the genetic diseases of Rodrigues (Section VII) where a geographical and historical background of this smaller island is presented. Réunion, the third member of the Mascarene group, is Mauritius' closest neighbour, lying 100 nautical miles to the West. It is, however, a French colony, independent from Mauritius and did not form part of the investigation.

Fig. 3-1: The Island of Mauritius.

Coral reefs which encircle Mauritius provide several harbours and a natural protection from the ocean swell. A ring of mountains, the highest reaching 1000 m, surrounds a central plateau of 600 m elevation. There are no major geographical barriers and the early settlers were able to gain free access to all sections of the island, regardless of their landing site.

Fig. 3-2: The Mascarene Islands: Réunion, Mauritius and Rodrigues.

Mauritius is often hot, damp and humid; mosquitoes thrive in this environment and malaria outbreaks are a constant threat. In summer, the Island's climate precludes sustained effort and the ability to perspire is a requisite for survival! (paragraph 19.2). Annual cyclones influence both the life and culture of the inhabitants, sometimes with disastrous consequences and multiple fatalaties. Memorable years often become historical reference points and all are given women's names!

There are no poisonous or dangerous animals on the Island. The genetic implications of isolation are reflected in a number of local species of flora and fauna that are unique to Mauritius (Durrel, 1977). A well-known example was the dodo, a large, flightless, friendly bird, found nowhere else in the world and rendered extinct since (and because of) man's arrival on Mauritius in the 17th century. Man, a natural disaster, devoured the hapless Dodo and significantly altered the Island's gene pool in this respect!

3.2 HISTORY

Throughout the three and a half centuries since explorers first landed on Mauritius, the Island's history has been marked by political and social turbulence. These dramatic and rapid changes were essentially the result of a struggle for Indian Ocean supremacy between the powerful sea-going nations of the Western world in their quest for a passage to the East. The monographs of Toussaint (1977), Hollingworth (1965) and Lenoir (1974), provided the historical facts from which the following brief account is derived.

3.2.1 The Dutch (1598-1710)

Although the Portuguese landed and explored Mauritius in the early 16th century, they did not settle there, as the Island lay off the normal route to the East. The Dutch, arriving in the Indian Ocean later that century, met with hostility between Africa and India and re-routed via the Mascarenes. They landed on Mauritius in 1598 and named the Island in honour of their Stadthouder, Maurice of Nassau, (Fig. 3-3). In order to forestall possible French and English occupation, the Dutch attempted to establish a colony, using chiefly convicts and slaves. The plan failed. From 1664 fresh expeditions with a succession of leaders arrived, including Fredrik Wreede (mentally unstable), Lamotius (autocratic and violent) and Hugo (a reformed pirate and incapable of discipline). In 1710 the Dutch abandoned Mauritius, blaming cane-eating rats for their failures although they could probably be more accurately attributed to poor administration

and a marked scarcity of women colonists. The latter problem, also encountered on Rodrigues (see Section VII) bore only one advantage: pirates were little attracted to Mauritius and plagued neighbouring Réunion instead!

Fig. 3-3: Maurice of Nassau

3.2.2 The French (1722 - 1810)

Already in formal possession of Réunion and Rodrigues, the French established rule of the Indian Ocean Islands by the colonisation of Mauritius in 1722. Many surnames of present day Mauritians date back to these original settlers. The establishment of the sugar industry necessitated the introduction of slaves and suitable males were purchased from Madagascar and East Africa. A census in 1766 revealed a total of 18,000 African slaves and 1,998 'Whites' and 'free men', (individuals who were neither European nor slave). The development of shipping and coffee required further manpower and by 1788 the 'Whites' and 'free men' totalled 6,913 - mostly an expansion of the original population, plus a small new input of Indian labourers who fell into the latter category - and 35,915 slaves. During this period 10,000 additional black men and women had been acquired from the East African coast.

In March of 1790, a ship brought news of the French Revolution. August Joseph d'Agnel de Assigne de Bourbon and his family, French aristocrats fleeing from the guillotine, were on board the "Mascareynes". Apparently unbeknown to them, the family carried the gene for Huntington Chorea. This example of the founder effect produced, at one stage, a prevalence of Huntington Chorea on Mauritius that was amongst the highest in the world (see Chapter 22.1).

French slavery and slave trading was officially abolished in 1794. However, free Mauritians were perturbed by the reports

of subsequent problems in the Haitian Negro republics and refused to abandon the practice. Their slaves were isolated and kept under careful surveillance. Trading prohibitions prevented any further acquisition of slave labour but, nonetheless, the slave population increased by over 50% to 65,672 during the next thirty years.

3.2.3 The British (1810 - 1968)

Slavery was one of several issues that led to discord between Mauritius and France and a rebellion against the Home Government. This opportunity was seized by Britain and resulted in their final capture of the Mascarenes in 1810. Three years later, in an administrative bungle, Réunion, instead of Mauritius, was restored to France and Mauritius and Rodrigues ceded to the British. So began a rule of 150 years.

With slavery finally abolished in 1813 a process of Anglicisation was initiated. Conversion of Mauritius to a British way of life and character met with resistance; no influx of British settlers occurred and Cape wine was spurned in favour of the French variety, despite duty free benefits. French language and culture persist to this day.

The sugar boom in the early stages of British rule had consequences which were destined to have a considerable influence upon present day Mauritius. A new class emerged in the form of elitist and separatist sugar planters and dealers. These "barons", in search of a work force, turned

to India. Between 1829 and 1909, 450,000 Indians, mostly Hindu, were indentured and Mauritius was in effect, Indianised. The population now became divided into Creoles (born on the Island) and Immigrants (newly arrived).

Malaria and cholera, hitherto absent on Mauritius, were introduced to the Island during this period and great epidemics of both diseases occurred at regular intervals. Indeed, between 1866 and 1868 there were 50,000 deaths from malaria alone. The gene for sickle cell anaemia conferred considerable heterozygous advantage to the recently freed African slave population and to many members of the Indian community. The genetic implications of this effect are evident in the current high incidence of homozygous sickle cell disease on Mauritius, notwithstanding the virtual eradication of malaria since 1952.

The cholera epidemic had an interesting effect on the small Chinese community. Only 2 of almost 2,000 Chinese died in the cholera crisis of 1854, although this epidemic killed 3,492 persons in Port Louis alone. While many citizens had to flee the capital, the Chinese were able to stay and their numerical prominence in this city remains evident today. Tea and opium were thought to have granted immunity, as both these commodities were used infrequently by the other communities.

Whether this protective factor was genetic or environmental remains unclear, but in either event it had a profound influence on the demography of the Island.

In 1909 Indian immigration was halted. A second sugar boom brought a new influx, this time not of indentured labourers but of Chinese shopkeepers from Canton and business men from Southern India.

At the beginning of this century, a series of devastating cyclones and fires hit Port Louis. By the Second World War, the effects of the cholera, malaria and small pox epidemics and a decline in the sugar industry, coupled with improved sea and air links, led to a steady emigration of families, who were socio-economically capable of leaving, to Australia, Europe and South Africa. By 1939, an estimated 16,000 Mauritians were in Durban alone, including *en passant*, the gene for Huntington Disease.

3.2.4 Present Era (1968 -)

Independence was proclaimed in 1968. Health care has greatly improved over the last few decades with primary and preventative medicine receiving special emphasis. Stringent public health regulations have kept Mauritius almost malaria-free. In the near future, the relative contribution of genetic disease is expected to play a significant role in morbidity, mortality, health care and planning.

To conclude this chapter, a summary of historical events and their possible genetic implications are listed in Table 3-1.

YEAR	EVENT	IMPLICATIONS
1598	Colonisation by the Dutch.	Dodo rendered extinct.
1710	Abandoned by Dutch.	No settlers remain.
1721	French occupation.	Mainly of Huguenot stock.
1766	Sugar industry established.	Introduction of Black Slave labour - 18,000 Madagascans.
	Development of coffee & shipping.	Introduction of 10,000 East African slaves.
1790	News of French Revolution.	The arrival of French aristocracy.
1794	Abolition of slavery in France.	Slave trading prohibited.
	Slave isolation and incarceration continues in Mauritius until 1835.	"Slave" population increases by 51% with minimal additional external input.
1810	Britain captures Mauritius.	An Anglicisation process fails.
1825	The sugar boom.	Indentured Indian work force.
1909	Indian immigration of 450,000.	Epidemics of malaria.
	Second sugar boom.	Immigration of Chinese and South Indian businessmen.
1939	Improved air and sea links.	A steady emigration of socio-economically privileged residents.
1958	Eradication of malaria.	No further heterozygote advantage for the sickle cell gene.
	Development of primary health care and medical services.	Decrease in incidence of infective diseases.

Table 3-I: Historical events and their possible implications for the presence of genetic diseases on Mauritius (1598 - 1987).

CHAPTER FOUR

DEMOGRAPHY, POPULATION AND CULTURE

4.1 INTRODUCTION

A meaningful assessment of the presence and impact of genetic disease in a community requires certain background demographic detail. Information concerning population size and rate of growth is necessary for the analysis of prevalence figures and the planning of health care. The impact of inherited disorders on the health of the community can be assessed from the major causes of morbidity and mortality. In addition, awareness of cultural differences and varying attitudes to issues such as marriage, birth, handicap and death have relevance in counselling, intervention and prevention. In this chapter demographic and cultural considerations for Mauritius are presented and discussed.

4.2 MAJOR CULTURAL GROUPS

Mauritius is a *pot-pourri* of races, religions and cultures. This diversity has arisen from the Island's position in the Indian Ocean which places Mauritius within the influence of three different civilisations - the African, the European and the Asian. The diverse origins of the present day Mauritian is reflected in the languages on the Island. Whereas the official tongue is English, French is predominantly spoken, although the language of the people, the *lingua franca*, is Creole.

Sociologically, the population is broadly divided into three communities - the Indo-Mauritian, the Chinese Mauritian and the General Population.

4.2.1 The Indo-Mauritians

The Indo-Mauritian community comprises approximately 525,000 Hindus and 170,000 Muslims.

The Hindus were, in the main, the Island's original field workers. This community became the majority population group within one generation after their arrival, a position they have held to this day. The Muslims, are the second largest religious group. Consanguinity is found in many families on Mauritius but is particularly common in this community.

Certain beliefs attributed to the Indo-Mauritian culture, could have an influence on the distribution, prevalence and management of genetic diseases. These factors include

acceptance of arranged marriages and consanguinity within certain groups, reservations regarding the use of birth control methods, opposition to the termination of a pregnancy and alcohol abstention (see paragraph 14-10).

4.2.2 Chinese Mauritian

Chinese culture is an integral part of Mauritius. The first Chinese settlers arrived in the latter half of the last century and were chiefly traders and shop keepers. By 1901 a slow immigration increased the Chinese population to a total of 3,515. Records indicate that only 58 of these persons were female (Appendix E.) This disparity in the genders may well have influenced the contribution of oriental genes that constitutes the Creole blend!

A curious and unexplained resistance to cholera during the lethal epidemics in Port Louis in 1854 helped establish a Chinese community in the capital city, a feature still present today. Marriage tends to be within the cultural group and parental influence is traditionally powerful although, with most young adults now second generation Mauritians, cultural ties are weakening. Roman Catholicism has replaced Buddhism in many families and success in business has hastened the move towards a Western life-style.

4.2.3 General Population

The General Population consists of some 250,000 individuals, broadly divided into 'Creoles' and 'Whites'. The Creoles' forebears were essentially the original African slaves with the admixture of many nationalities including the Franco-Mauritian, Chinese and Indian communities.

The 'Whites' are predominantly descendants of French colonists, who came to Mauritius some five generations previously. They have formed a close community and almost all of today's Franco-Mauritians can claim to be related to each other! The Franco-Mauritian group shows the least population growth (Fig. 4-1) due to a high rate of emigration, either to obtain further education or in times of political uncertainty or socio-economic instability. This mobility can influence the incidence and prevalence of inherited disorders significantly as emigration tends to be by family unit with the potential to eradicate a faulty gene from the Island (see cystic fibrosis, paragraph 19.7). In addition, following tertiary education abroad or a perceived change in the socio-political circumstances, young adults may return to the Island, sometimes accompanied by spouses of a different nationality.

The General Population holds predominantly Catholic beliefs and adheres to Papal directives concerning the preservation of life, contraceptive methods and other issues that are relevant in genetic counselling.

4.3 POPULATION STATISTICS

4.3.1 General

During 1986 the total population of Mauritius reached one million. The Mauritian census of 1983 did not include a population group analysis but Lenoir, in 1985, considered the Chinese Mauritians to number about 30,000, with a Muslim community of about 170,000 and the Hindus consisting of over 525,000 people. The remainder of the populus falls under the appelation of 'General Population'.

A spectacular population growth rate has occurred on Mauritius since the introduction of the indentured labour force in 1846. Today, the Island has one of the highest population densities in the world; the estimated 1,387 individuals per square mile is double that of Britain. The comparative population growth curves from 1846-1985 are depicted in Fig. 4-1.

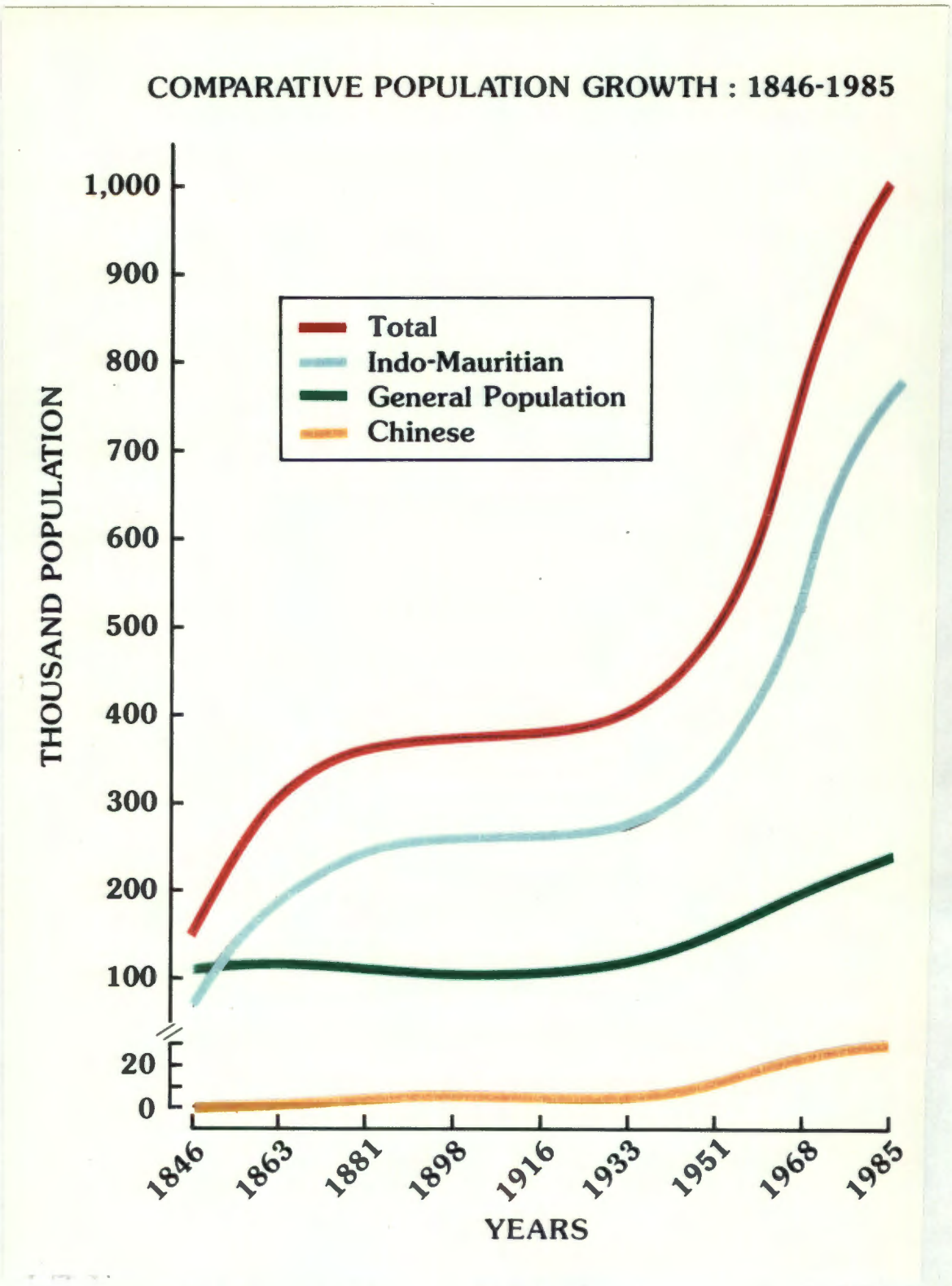

Fig. 4-1: Comparative Population growth: 1846-1985.

4.3.2 The Influence of Disease on Population Growth

An insular community like Mauritius is vulnerable to sweeping epidemics of infectious diseases. The cholera crisis of 1854 killed 3,492 people in Port Louis alone. In 1891, 650 Islanders succumbed from smallpox. There were 31,920 cases of malaria during 1867/8 and at the peak of the rainy season this disease was responsible for up to 200 deaths per day in Port Louis alone. By 1918 the death rate for Mauritius was 40 per thousand mainly due to malaria.

The control and eradication of infectious diseases has played a major role in doubling the population of Mauritius over the last thirty years; indeed, 41,9% of the mid-1985 population was under the age of twenty. The population and vital statistic rates for the Island since 1921 are correlated in Table 4-I. In Table 4-II and Table 4-III the principal causes of deaths in infants are listed (Brissonnette, 1986).

Analysis of the Mauritian demography highlights several points. In the presence of improved health care, especially in the area of infectious disease control and perinatal mortality, the population is growing rapidly. In the future an increase in the relative contribution of inherited disorders to morbidity and mortality can be anticipated. These circumstances on Mauritius provide a background for the survey into inherited disorders that is presented in the following sections.

Period	Population at Mid-period	Crude Birth Rate	Crude Death Rate	Rate of Natural Increase	Infantile Mortality Rate[1]	Still Birth Rate[2]
1921-25 Average	379,636	39.1	31.0	8.1	141.8	96.3
1926-30 "	403,248	35.2	28.8	6.4	140.9	81.2
1931-35 "	398,647	31.3	29.8	1.5	140.3	88.7
1936-40 "	412.003	33.1	27.1	6.0	155.6	83.4
1941-45 "	417,838	36.0	28.5	7.5	154.3[3]	76.2
1946-50 "	438,797	44.7	20.8	23.9	119.6[4]	64.4
1951-55 "	522,277	44.3	14.7	29.6	81.3	59.7
1956	574,938	43.3	11.7	31.6	66.0	67.0
1957	593,070	42.6	12.8	29.8	75.1	66.5
1958	609,518	40.4	11.7	28.7	67.4	64.7
1959	627,249	38.1	10.8	27.3	62.5	68.5
1960	644,743	39.3	11.2	28.1	69.5	65.8
1961	662,368	39.4	9.8	29.6	62.0	70.0
1962	681,619	38.5	9.3	29.2	60.1	65.5
1963	695,641	40.2	9.6	30.6	59.3	51.5
1964	716,298	38.4	8.6	29.8	56.7	55.3
1965	735,245	35.7	8.6	27.1	64.1	55.9
1966	753,276	35.6	8.9	26.7	64.2	49.1
1967	767,782	30.6	8.5	22.1	70.5	43.7
1968	781,615	31.2	9.1	22.1	69.1	43.5
1969	792,893	27.4	8.1	19.3	70.4	41.9
1970	805,489	26.8	7.8	19.0	57.0	38.1
1971	816,561	25.5	7.7	17.8	51.7	38.8
1972	826,199	24.8	7.9	16.9	63.8	33.8
1973	846,089	22.4	7.7	14.7	63.3	34.5
1974	857,063	26.8	7.3	19.5	45.6	35.9
1975	867,824	24.8	8.0	16.8	48.7	40.0
1976	879,193	25.3	7.8	17.5	40.4	34.0
1977	893,069	25.5	7.8	17.7	45.0	30.4
1978	907,779	26.7	7.1	19.6	33.9	26.2
1979	922,807	27.2	7.2	20.0	32.9	25.3
1980	937,886	26.6	7.1	19.5	32.3	24.3
1981	950,785	24.9	6.7	18.2	33.6	22.8
1982	960,994	22.1	6.6	15.5	29.4	20.2
1983	968,609	20.6	6.5	14.1	25.6	18.6
1984	977,129	19.7	6.6	13.1	23.1	19.8
1985	985,210	18.8	6.8	12.0	23.8	19.5

TABLE 4-I: Population and vital statistics rates for the Island of Mauritius (1921-1985).

NOTES

1. Deaths of children under 1 year of age per 1,000 live births.

2. Still births per 1,000 total births (live births and still births).

3. The rate reached 188.0 in 1945 when there were poliomyelitis and dysentery epidemics.

4. The rate reached 186.2 in 1948 when there was an epidemic of whooping cough.

CAUSE (ICD 1975 Revision)	DEATHS	
	Number	% of Total
Slow fetal growth, fetal malnutrition and prematurity	121	38.8
Hypoxia, birth asphyxia and other respiratory conditions	116	37.2
Congenital anomalies	30	9.6
Septicaemia and infections specific to the perinatal period. e.g. tetanus neonatorum	23	7.4
Haemolytic disease of newborn due to isoimmunization and other perinatal jaundice	3	1.0
Fetal and neonatal haemorrhage	2	0.6
Sudden infant death syndrome	2	0.6
All other causes	15	4.8
TOTAL	**312**	**100.0**

Table 4-II: Principal causes of neonatal deaths - 1985 (deaths under four weeks).
(ICD = International classification of diseases)

CAUSE (ICD 1975 REVISION)	DEATHS	
	Number	% of Total
Ill-defined intestinal infections (colitis, enteritis, gastro-enteritis, diarrhoea)	25	19.4
Pneumonia	24	18.6
Congenital anomalies	12	9.3
Septicaemia and infections specific to the perinatal period	8	6.2
Bronchitis	7	5.4
Slow fetal growth, fetal malnutrition and immaturity	7	5.4
Meningitis	3	2.3
Accident caused by fire	2	1.6
Asthma	2	1.6
All other causes	39	30.2
TOTAL	**129**	**100.0**

Table 4-III: Principal causes of post-neonatal deaths - 1985

(deaths between four weeks and one year)

SECTION III

INHERITED DEAFNESS ON MAURITIUS

An aetiological study of deafness on the Island of Mauritius is presented and discussed with special emphasis placed on the contribution made by genetic disease.

Chapter 5: Genetics and Deafness: General Background.

Chapter 6: Methodology for the survey of deafness on Mauritius.

Chapter 7: Deafness on Mauritius: Findings.

Chapter 8: Deafness on Mauritius: Discussion.

CHAPTER FIVE

GENETICS AND DEAFNESS: GENERAL BACKGROUND

5.1 INTRODUCTION

Deafness has a devastating effect on a child's development. Defective hearing and the inability to develop normal speech impede all contact with one's fellow man.

Profound childhood deafness may affect 1:1000 individuals in economically advanced populations and the prevalence may be even higher in the developing communities (Fraser, 1976). The contribution of genetic disease to this total is known to be significant but varies according to investigator, institution and country of study. The number of people handicapped by deafness on Mauritius is unknown and the contribution of genetic disorders to hearing loss on this Island is hitherto undocumented.

Analysis of the causes of deafness in a community is an essential first step for any programme that aims at prevention and early detection of those at risk. In addition, this information is required for the formulation of appropriate education and rehabilitation. Section III is concerned with genetic disease and deafness on Mauritius. The background against which the methodology was devised is presented in this chapter.

5.2 THE CLASSIFICATION OF DEAFNESS FOR SURVEY PURPOSES

Deafness can be classified into three broad categories:

1. Genetic
2. Acquired
3. Cryptogenic

A brief description of each category is presented below and detailed further in the discussion (Chapter 8).

5.2.1 Genetic Deafness

Genetic deafness is usually present at birth although in some instances it may manifest in later life. As with all forms of hearing loss, a broad division into 'conductive', 'sensorinueral' and 'mixed' deafness can be made on audiometric characteristics. An accurate clinical diagnosis, if this can be achieved, plus a family history demonstrating the mode of transmission and the recognition of any associated syndromic stigmata are crucial in the diagnostic process.

Positive information along these lines of investigation will afford the further classification of genetic deafness into:

i) Recognizable genetic syndromes.

ii) Familial undifferentiated deafness: AD, AR, XL.

5.2.2 Acquired Deafness

Although a carefully constructed case history will frequently permit allocation of acquired status to an obvious case, the situation, especially with congenital deafness, is not always clear cut. The action of environmental agents causing deafness during intra-uterine and perinatal life may occur unobserved and further blurring of the borders between 'genetic' and 'acquired' emerges when genetic components to foetal susceptibility are considered. For example, Anderson et al (1970) suggest a genetic vulnerability of the hearing mechanism to maternal rubella infection and Viljoen et al (1983) describe an autosomal dominant oto-sensitivity to streptomycin in the treatment of tuberculosis.

5.2.3 Cryptogenic Deafness

By excluding genetic and well-defined acquired causes of deafness, investigators are left with a significant 'unknown' or 'cryptogenic' group. It is probable that many of these unknowns have a genetic basis (Taylor et al, 1975). Many sporadic cases are probably familial: for example, sons of carrier mothers with XL conditions, new mutations for AD disorders and an only child with homozygosity for AR disease. Any assessment of the contribution of genetic disease to congenital deafness is likely, therefore, to be an underestimate.

With time, the birth of further affected siblings or progeny might assist in reclassification of these individuals and it

can be foreseen that medical progress will eventually reveal the true nature of the rest.

For the purposes of the Mauritian survey a distinction is drawn between cryptogenic deafness without additional abnormalities and those patients with clinical features that might be of associative importance.

CHAPTER SIX

METHODOLOGY FOR THE SURVEY OF DEAFNESS ON MAURITIUS

6.1 THE ASCERTAINMENT OF DEAF INDIVIDUALS

Deaf individuals included in this study were ascertained from the following sources:

6.1.1 The School for the Deaf

The School for the Deaf was opened in 1969. It caters for the 3-18 age group and at present has an attendance of between 60 and 70 children (Fig. 6-1). Criteria for admission include normal intelligence and reasonable visual acuity; physical handicap is not necessarily an exclusion criterion. The waiting list is long and preference is given to younger children.

Fig. 6-1: School for the Deaf.

All children were assessed according to the protocol in 6.2. Medical information and the results of audiometric testing when available were documented and evaluated in conjunction with the clinical examination. In the history taking, special emphasis was placed on genealogy and details of perinatal events; the latter however were frequently difficult to clarify.

Systematic clinical evaluation was performed with particular attention paid to the fundi, cardiac auscultation and the possibility of subtle yet specific syndromic associations.

Selected individuals underwent further special investigations at the local hospital, including radiography, additional audiometry and electrocardiography.

6.1.2 Pre-Primary Schools

Pressures on the limited vacancies for admission to the School for the Deaf has necessitated the establishment of an alternative educational programme. Selected primary schools admit deaf children in the under-five age group into the pre-primary classes and attempt to main stream and integrate them with the normal teaching at an early stage. This is a new approach and the few children involved were assessed as in 6.1.1.

6.1.3 Logopaedic Services

The logopaedic service on Mauritius is provided by a single individual, at a specialised ENT hospital. Perusal of her records resulted in the referral of families or individuals where deafness or defective hearing appeared to have a genetic component. Children with oro-facial clefting, those with associated mental handicap and patients with partial hearing loss who therefore did not fit the criteria for admission to the deaf schools were obtained from this invaluable service.

6.1.4 Individual Referrals

For geographical, social and economic reasons many deaf children are kept at home. The incidence of "hidden at home" deafness on Mauritius is probably higher than other handicapping disorders; these children are useful around the house, can be domestically trained and do not become victims of institutional dumping.

Persons referred from local specialists and health care workers were assessed on an individual basis. In these patients, as with many others, home visits were undertaken when further genealogical or medical information was required.

6.2 DIAGNOSTIC SCREENING OF THE DEAF CHILD

The following approach is taken from a diagnostic evaluation formulated by Beighton and Sellars (1982) following their considerable experience in this particular field. It is presented here as the screening protocol on which the Mauritian study was based.

Case History: Prenatal : Maternal illness, chemotherapy.
Perinatal : Anoxia, trauma, jaundice.
Postnatal : Ototoxic drug therapy, including aminoglycosides for burns.
Serious illness.

Age of onset and rate of progression of deafness.
Age of commencement of speech.

Family History: Including parental consanguinity, advanced paternal age and affected relatives.

Clinical Examination: Full examination for syndromic associations; ophthalmological assessment and cardiac auscultation warrant special attention.

Audiometric Studies:

Further Special Investigations: These may include:

Radiography

Renal or metabolic assessment

Serology

ECG

EEG

Cytogenetic studies

CT scanning

6.3 LABORATORY FACILITIES

The serological investigations, cytogenetic services, molecular facilities and specialised imaging techniques employed in similar surveys in more developed communities are not yet available on Mauritius. Screening for renal disease, endocrine dysfunction and chromosomal abnormalities have a low yield in genetic deafness and were considered inappropriate in this setting. However, because of the academic nature of this first survey, selected individuals were chosen for cytogenetic assessment and a large deaf family was singled out for molecular linkage studies. (X-linked deafness of Nance; see chapter 22).

These investigations were performed by the molecular laboratories of the Department of Human Genetics at the University of Cape Town, during phase III of this project.

CHAPTER SEVEN

DEAFNESS ON MAURITIUS: FINDINGS

7.1 INTRODUCTION

The clinical findings in 116 Mauritian individuals are discussed in this chapter. Sixty three children attended the School for the Deaf, 5 were in the pre-primary classes, 25 were detected from perusal of hospital and logopaedic records and 23 persons were ascertained from individual referrals.

Attention is also drawn to persons where deafness, although present and profound, was not considered the major handicap by virtue of its association with additional abnormalities. Categorisation in these instances can be difficult but criteria based upon the education of the individual were considered to be of most relevance. If a child with multiple handicap could maximally benefit from an education in a school for the deaf, he or she was included in the statistics for deafness.

Sixty seven individuals were male and 49 were female; the ethnic breakdown is shown in Table 7-I, aetiologies are presented in Table 7-II and each category of deafness is further analysed in this chapter.

ETHNIC GROUP	NO.	%
Hindu	68	59%
General Population	23	20%
Muslim	10	8,5%
Tamil	6	5%
Chinese	3	2,5%
Documented	6	5%
TOTAL	**116**	**100%**

Table 7-I: Analysis by ethnic group of 116 deaf individuals on Mauritius.

CATEGORY	TOTAL	%
Syndromic	34	(30%)
Familial	20	(17%)
Acquired	12	(10%)
Cryptogenic	50	(43%)
TOTAL	**116**	**(100%)**

Table 7-II: Aetiological analysis of deafness in 116 individuals.

7.2 SPECIFIC SYNDROMES

Genetic syndromes encountered during the survey are shown in Table 7-III:

SYNDROME	MODE OF INHERITANCE	TOTAL
Oculoauriculovertebral dysplasia	AD/AR	6
Otosclerosis	AD	6
Waardenburg syndrome	AD	5
Osteogenesis imperfecta	AD	1
Treacher Collins syndrome	AD	1
Enchondromatosis with dwarfism	AR	1
Deafness of Nance	XL	14
TOTAL		**34 (100%)**

Table 7-III: Genetic deafness syndromes on Mauritius.

7.3 UNDIFFERENTIATED FAMILIAL DEAFNESS

In certain deaf individuals, with no additional syndromic stigmata, there was a family history of deafness or close parental consanguinity. Affected individuals could be allocated to a specific mode of inheritance without differentiation into a known genetic entity. Twenty cases fell into this category - 9 males and 11 females - representing 42,5% of the total for known genetic deafness.

Sixty percent of persons with undifferentiated familial deafness were progeny of first or second cousin marriages. No instances of undifferentiated AD deafness were found.

7.4 ACQUIRED DEAFNESS

Twelve individuals were assessed as having deafness of non-genetic aetiology, representing 10,3% of the 116 deaf individuals in this survey. They are included in this chapter to illustrate the contribution of acquired disease towards deafness. Only those persons with clearly documented histories of environmental insult are included in Table 7-IV. Any doubtful cases have been categorised as "unknown".

ONSET	CAUSE	TOTAL
Prenatal	Rubella	3
Perinatal	Hyperbilirubinaemia	4
	Anoxia, prematurity	2
Postnatal	Meningitis	1
	Middle ear disease	2
TOTAL		12

Table 7-IV: Acquired causes of deafness in 12 individuals.

7.5 CRYPTOGENIC DEAFNESS

From a total of 50 individuals with deafness of unknown or cryptogenic aetiology, 29 had no additional abnormalities. A wide range of non specific concomitant features were present in 21 persons (42%); examples of the more common anomolies are represented in Table 7-V and depicted in Fig. 7-1 and Fig. 7-2. This large group remains the focus for future academic pursuit and clarification and has important practical significance in the classification of genetic deafness.

CLINICAL FEATURES	TOTAL
No dysmorphology	29
Branchial pits	1
Broad thumbs	1
Cardiac murmur	4
Cleft lip/palate	2
Facial asymmetry	3
High arched palate	2
Malar hypoplasia	1
Micrognathia	2
Skin depigmentation	2
Structural helical abnormalities	1

Table 7-V: Details of concomitant findings in cryptogenic deafness.

Fig. 7-1:

Dysmorphisms in cryptogenic deafness: skin depigmentation in the lateral boys (above) and facial asymmetry in a young girl (left).

Fig. 7-2:
Dysmorphisms in cryptogenic deafness: simple helix and low slung ears (above) and malar hypoplasia (left).

7.6 DEAFNESS AS AN ADDITIONAL HANDICAP

When planning future management of a multi-handicapped child, his or her deafness may in fact be considered a secondary difficulty. As indicated in paragraph 7.1, additional handicapping, especially blindness and mental retardation, significantly alters the approach to education and rehabilitation of the deaf child. For the sake of completion, an analysis of 14 children in whom deafness was an additional handicap is presented in Table 7-VI; these cases are documented in their relevant sections and not included in the analysis of individuals with deafness.

MAJOR DISABILITY	DIAGNOSIS	MODE OF INHERITANCE	TOTAL
Mental handicap	Unspecified metabolic disorder	AR	2
Mental handicap	Neonatal hyperbilirubinaemia	Acquired	1
Mental handicap	Cerebral palsy	Unknown	5
Mental handicap	Trisomy 21	Chromosomal	2
Physical handicap	Meningo-encephalitis	Acquired	1
Blindness	'Severe illness'	Acquired	1
Blindness	Rubella	Acquired	1
Mental handicap	Perinatal anoxia	Acquired	1

Table 7-VI: Causes of deafness in 14 children with multiple handicap.

7.7 THE SCHOOL FOR THE DEAF

Finally, the causes of deafness found in the 63 children at the School for the Deaf are presented independently (Table 7-VII). This additional analysis facilitates comparison with similar studies from other centres as the ascertainment of the sample is standardized by the generally accepted criteria for admission to schools for the deaf.

CATEGORY	TYPE	M	F	TOTAL (%)
Syndromic	Waardenburg	1	-	1
	Oculoauriculo-vertebral dysplasia	1	3	4
	Osteogenesis Imperfecta	1	-	1
	Spondyloenchondro-matosis	-	1	1
	TOTAL	3	4	7 (11%)
Familial	AD	-	-	-
	AR	5	6	11
	XL	4	-	4
	TOTAL	9	6	15 (24%)
Cryptogenic		21	13	34 (54%)
Acquired	Rubella	1	2	3
	Prematurity, hypoxia	-	1	1
	Hyperbilirubinaemia	-	2	2
	Middle ear disease	1	-	1
	TOTAL	2	5	7 (11%)
GRAND TOTAL		**35**	**28**	**63 (100%)**

Table 7-VII: Causes of hearing loss at the School for the Deaf.

CHAPTER EIGHT

DEAFNESS ON MAURITIUS: DISCUSSION

8.1 INTRODUCTION

The incidence of deafness on Mauritius is unknown. In this survey, 116 individuals with profound deafness were assessed. As the aim of the study was to determine the presence and minimum prevalence for inherited deafness this sample gained a genetic bias regarding referrals from local medical professionals. However, all available students at the School for the Deaf were screened and this group is thus representative for the category of profound childhood deafness on Mauritius and affords comparison with the findings of similar studies in other communities (Taylor et al, 1975; Sellars et al, 1975; Sellars et al, 1976; Sellars and Beighton 1983; Beighton et al, 1987).

In many developed countries, the incidence of inherited disorders as a cause of severe deafness is greater than 50%; a contribution that appears to be increasing as health care improves (Chung, 1970). On Mauritius, 54 of the 116 deaf persons had a genetic cause (46,5%); this aetiology was present in 22 out of 63 children at the School for the Deaf (34,9%). The incidence of acquired causes, appears to be similar to that recorded in other studies, with no significant or unusual findings. (Sellars et al, 1976; Sellars and Beighton, 1983). Certain features of island communities, namely the founder effect and consanguinity make a significant contribution to deafness on Mauritius. In

addition, certain syndromes were notable by their absence. These important details are discussed in this chapter, each under their respective headings.

8.2 SYNDROMIC DEAFNESS

Known syndromes accounted for 30% of deafness encountered in the survey, a higher figure than the 10% generally quoted for this category. Two reasons may contribute to this finding:

(i) The island setting enabled a comprehensive investigation of a proband's family to be undertaken and further affected members were then included in the total for syndromic deafness.

(ii) Large families with syndromic deafness (otosclerosis, X-linked deafness of Nance) demonstrated a founder effect and greatly increased the contribution of this category as a cause for deafness on Mauritius.

If the figures for the Deaf School are considered, syndromic deafness accounts for 10% of the students. The sampling in this instance has closer correlation with other surveys as only the proband is included and the founder effect is reduced.

The majority of the common genetic deafness syndromes were represented. It might have been expected that Pendred syndrome, said to have an incidence in the newborn of 7,5 per 10,000 in the United Kingdom (Fraser 1965) and representing 5% of children with syndromic deafness in some surveys

(Sellers and Beighton, 1983), would have been encountered. However, the later development of the goitre (mid-childhood) and the mildness of the hypothyroidism (if present) makes diagnosis in the screening milieu difficult in the absence of a positive family history. Clinical review of the younger persons with ostensibly undifferentiated deafness may in time reveal these cases.

Certain syndromic conditions which were encountered during the survey have been selected for brief discussion below.

8.2.1 Oculoauriculovertebral dysplasia (OAV)

The term "oculoauriculovertebral dysplasia" (OAV) embraces what might be a continuous spectrum of an heterogeneous disorder; problems lie in exact terminology and the minimal criteria for inclusion in the diagnosis. Gorlin et al, (1976) include the Goldenhar syndrome and hemifacial microsomia in the overall category of OAV. In a recent study of 294 patients with OAV, Rollnick et al (1987) promulgated the minimal diagnostic criteria of microtia, mandibular hypoplasia, anomalies of the cervical spine or lipodermoids - alone or in combination.

Due to the nature of this study and the small numbers involved, broad nosologic categorisation was considered valid. In so doing, OAV was a relatively common cause of syndromic deafness on Mauritius, accounting for 5% of deafness in the sample analysed. Two individuals representing either ends of the phenotypic spectrum are portrayed in Fig. 8-1.

Fig. 8-1:

Oculoauriculovertebral dysplasia:

A phenotypic spectrum encountered on Mauritius, from Goldenhar syndrome (left) to mildly affected hemifacial microsomia (below).

8.2.2 Autosomal Dominant Otosclerosis

Six persons from a two generation family had AD otosclerosis. This genetic deafness syndrome is unusual in that the hearing loss is of a late onset. In addition, expression of the gene is variable and difficulties thus arise in counselling and molecular analysis. The founder effect may have influenced the contribution of otosclerosis to syndromic deafness on Mauritius.

8.2.3 X-linked deafness of Nance

In a large Hindu dynasty, 14 deaf males had a mixed hearing loss with stapes fixation and perilymphatic gusher at surgery. This rare form of X-linked deafness, originally described by Nance et al (1971), is the commonest cause of syndromic deafness on Mauritius! The implications of counselling, antenatal testing and the results of molecular linkage analysis for this family are discussed in the separate chapter dealing with genetic diseases of special significance to Mauritius (Chapter 22).

8.2.4 The Waardenburg syndrome

Five individuals in three families had features of Waardenburg syndrome, constituting 15% of the total for specific deafness syndromes. This interesting entity represents 40-50% of specific genetic deafness syndromes in other similar studies (Sellars and Beighton, 1983).

Difficulties arise in the ascertainment of individuals carrying the Waardenburg gene as deafness is a variable component to the syndrome, present bilaterally in 10-20% of affected persons and unilaterally in approximately 5% (Sellars and Beighton, 1983a).

Three siblings from a Mauritian family with Waardenburg syndrome are depicted in Fig. 8-2. Only the boy is deaf although all three have heterochromia. A grey forelock is present in the older sister. Both parents had normal hearing and eye colour but the father developed premature greying of his hair in early adulthood. He is presumed therefore to carry the gene but to demonstrate minimal phenotypic expression. The father did not have dystopia canthorum, a feature present in his three children.

Genetic heterogeneity and distinction into Waardenburg Type I and Type II based on the presence or absence of dystopia canthorum has been suggested (Arias, 1971); subsequently, variable expressivity rather than heterogeneity was postulated (Arias and Mota, 1978). Evidence in this family would support the latter theory.

Fig. 8-2:

Waardenburg syndrome:

A deaf boy and his two sisters, both with normal hearing.

8.2.5 Enchondromatosis with dwarfism and deafness

Spondyloenchondromatosis is a very rare condition in which enchondromatoses of the long bones are associated with variable abnormalities in the spine and dwarfism. Deafness has not previously been documented as a concomitant feature.

A ten year old girl with enchondromatoses and profound deafness attends the School for the Deaf. As this diagnosis is primarily made on radiological findings, a full description of this individual is presented in Chapter 17. However, deafness remains the major handicap and this case is thus mentioned in this section.

8.2.6 Treacher Collins Syndrome (Mandibulofacial Dysostosis)

Treacher Collins syndrome is considered separately from OAV (8.2.1) although both can be regarded as branchial arch anomalies. Treacher Collins syndrome, however, has a well documented AD inheritance, frequent bilateral involvement and a characteristic facial dysmorphology which distinguishes it from OAV.

This disorder, involving structures derived from the first branchial arch, groove and pouch, often symmetrically and with variable expressivity, was found in an infant of unaffected consanguineous parents (first cousins) (Fig. 8-3). In addition to documenting the presence of the gene, this case demonstrates how, in a family setting predisposing to AR disorders, accurate clinical assessment is required to correctly identify a new dominant mutation. This has significant bearing on the counselling for recurrence risks.

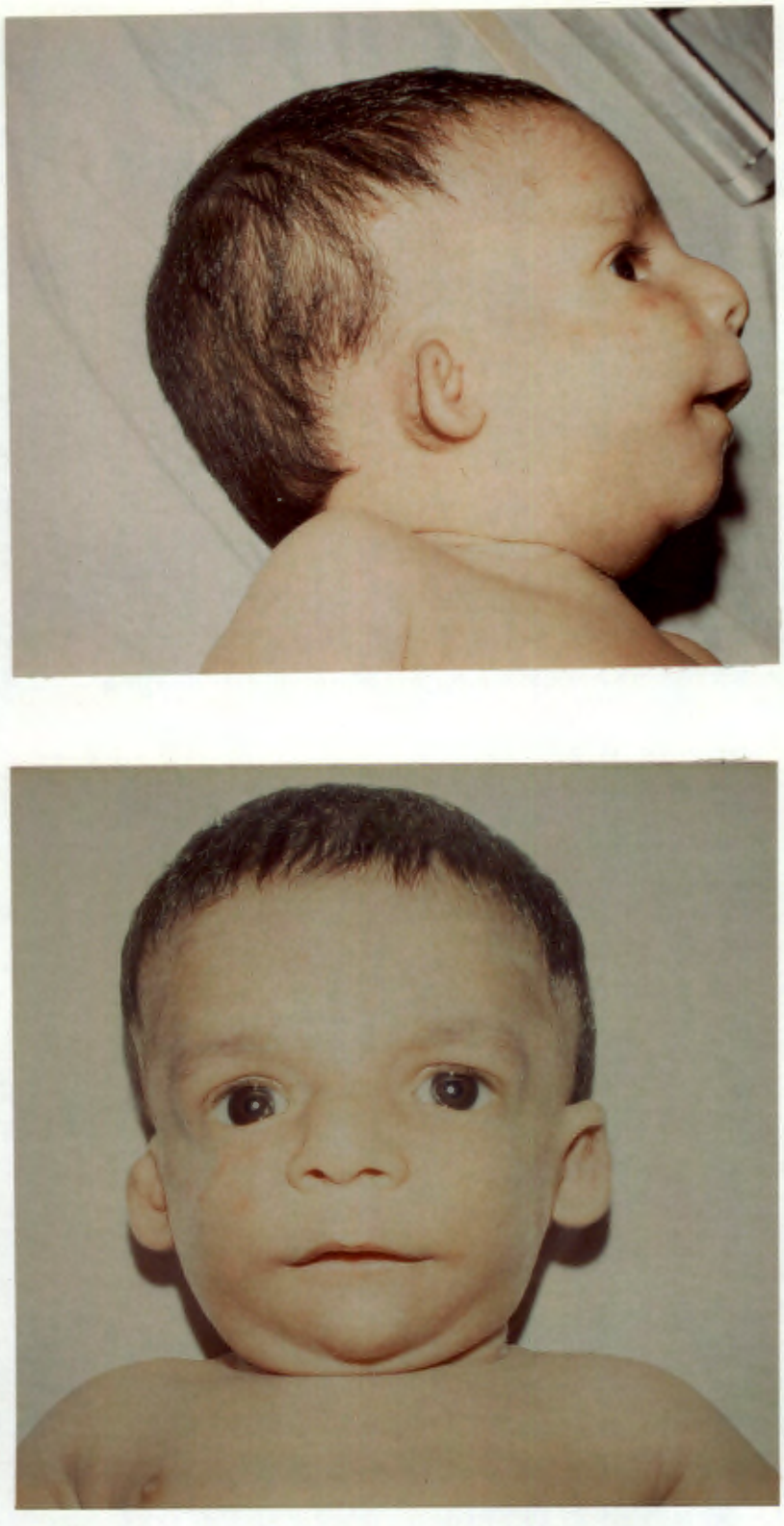

Fig. 8-3: Mandibulofacial dysostosis in an infant.

8.3 UNDIFFERENTIATED FAMILIAL DEAFNESS

Twenty of 116 individuals had clear evidence of undifferentiated familial deafness and represented 17% of the total and 42,5% of those with known genetic deafness. These figures are higher than similar studies in the UK (Fraser, 1976) and Southern Africa (Sellars and Beighton, 1983) where a total of 11% is quoted.

An unusual and unexpected finding was the absence of AD undifferentiated familial deafness. It is feasible that an AD deaf person would be selected against, when immigration to an island community either as labourer or overseer was considered (as opposed to the XL form where the carrier female is normal, or the otosclerotic family where deafness is of later onset).

Distinction between AR and XL inheritance was often unclear on the information available. When advice and counselling was given, AR risks were considered appropriate. Factors influencing this approach included: the Mauritian setting of isolation, the rarity of X-linked recessive deafness (Cremers et al, 1985) and the equal distribution of affected males and females for the category of undifferentiated familial deafness.

AR disease is an important cause of deafness on Mauritius. Consanguinity, confirmed in 60% of cases, plays a major rôle. An ethnic breakdown of the twelve consanguineous unions that resulted in AR deafness showed 6 Hindu, 3 Muslim, 2 Tamil and

one from the general population.

Consanguinity is generally considered to be more prevalent in the Muslim community and the relatively high proportion in persons of Hindu origin warrants emphasis. Although the figures are too small for statistical significance, they are of importance in the consideration of genetic counselling for cases of sporadic undifferentiated deafness. With recessive genes and consanguinity present in all the Indo-Mauritian communities, recessive risks may well apply to the unknown sporadic deaf individual at present categorised as cryptogenic.

8.4 CRYPTOGENIC (UNKNOWN) DEAFNESS

Forty-three percent of all deaf individuals had hearing loss of unknown aetiology. This figure is in keeping with other surveys and remains a similar diagnostic stumbling block to all investigators of deafness.

The documentation of concomitant non-specific features is of doubtful merit but is included to illustrate the range and frequency of these findings. Some, such as cleft lip, cardiac murmur, high arched palate, will probably with time prove to be genetically significant; ear pits are already part of a recognized syndrome (Bergstrom, 1979) but the absence of a family history in the case encountered on Mauritius precluded diagnostic precision.

8.5 ACQUIRED DEAFNESS

Acquired deafness was found in 12 individuals (10%). The strict criteria used in this study for inclusion in this category are probably responsible for the lower prevalence compared to other surveys +/- approximately 20% in the UK (Maran, 1966) 25% in Southern Africa (Sellars and Beighton, 1983). The nature of the acquired disorders revealed no unique or unexpected factors.

The thin line between 'genetic' and 'acquired' deafness has already been alluded to in paragraph 5.2.2. Frequently a disease process such as jaundice, perinatal anoxia or a 'severe illness' may have been incriminated and incorrectly enshrined in the individual's case records as the cause for his or her deafness. However, it might be considered that the magnitude of a perinatal insult (notably hyperbilirubinaemia and anoxia) sufficient to cause deafness, is likely to seriously damage other areas of the brain. Multiple handicap can then be expected with mental retardation overshadowing deafness.

It is notable that results of screening for deafness in other developing countries indicate a downward trend in acquired causes during the last ten years (Beighton et al, 1987). This presumably reflects the improvement in primary medical health care and a similar trend can be expected in Mauritius. Inherited disorders as a cause of hearing loss will then increase proportionately and accurate diagnostic categorisation with effective counselling will adopt an even higher profile in the prevention and management of genetic deafness on the Island.

SECTION IV

INHERITED BLINDNESS ON MAURITIUS

An aetiological study of blindness on the Island of Mauritius is presented and discussed with special emphasis placed on the contribution made by genetic disease.

Chapter 9: A survey of inherited blindness: Introduction and Methods.

Chapter 10: Results of an aetiological survey of 84 blind individuals.

Chapter 11: Blindness on the Island of Mauritius: Discussion.

CHAPTER NINE

A SURVEY OF INHERITED BLINDNESS:

INTRODUCTION AND METHODS

9.1 INTRODUCTION

Surgical and medical therapy has radically altered the contribution of different aetiologies to blindness over the last century. For example, in the 1800's, two thirds of the pupils attending the Liverpool School for the Blind had lost their sight due to smallpox; by the early 1900's, ophthalmia neonatorum was the overwhelming cause (Sorsby 1972). By 1952, the use of oxygen in the care of the premature infant resulted in retrolental fibroplasia being incriminated in 44% of blindness in newborns in 1952 (Fraser and Friedmann, 1967). Genetic disease is the commonest present day cause accounting for significant visual handicap in approximately 50% of cases (Jay, 1987).

The causative patterns of blindness vary, not only historically, but also geographically and socio-economically. In this chapter, the aims and methods of an aetiological survey into blindness on the Island of Mauritius are considered.

9.2 THE DEFINITION OF BLINDNESS

For educational purposes the definition of blindness must be flexible. Visual loss is frequently incomplete and therefore different categories of visual impairment occur within the same institution. For the purposes of this survey, acuities less than or equal to 3/60 (Snellen) were included. This criterion, in keeping with W.H.O. standards, facilitates comparison with similar studies. Parenthetically, the USA Internal Revenue Service, for Tax deduction purposes, defines blindness as "Central Visual Acuity of 6/60 or less", thereby including persons with Industrial Blindness (poor vision limiting occupation opportunities) and Automobile Blindness (inability to obtain a driving licence).

9.3 A SURVEY INTO THE CAUSES OF BLINDNESS

9.3.1 Ascertainment of Blind Individuals

Specialised institutions for blind persons provide the ideal setting for the study of the causative environmental and hereditary factors.

i) The Lois Lagesse Centre for the Blind

This institution admits approximately 70 blind individuals from the Island and is the only local institution catering for the visually handicapped. The educational programme is structured along the lines of a 'day-care centre' rather than a school. There is no upper age limit and some of the adults have attended regularly for many years. Transport to and from the Centre is a limiting factor for the blind persons residing in outlying areas. The sample was thus representative of blind individuals on Mauritius, between the ages of 5 and 45, who did not have a significant additional handicap.

ii) Individual Referrals

In assessing genetic causes of blindness, two groups of individuals were not adequately represented at the Centre for the Blind. They included children of pre-school age and those individuals with multiple handicap. Local practitioners were encouraged to refer patients with ophthalmological disorders which had a possible genetic basis and individuals from these two categories were thus investigated.

9.3.2 Methods

The following cardinal principles for the systematic screening of an institution for the blind were devised following general reading and personal experience:

i) The physical examination must be thorough; efficiency is enhanced by the examiner's awareness of likely concomitant features, for example, polydactyly and retinitis pigmentosa.

ii) Ophthalmological assessment is fundamental for accurate nosological delineation and is best performed by specialists in this field with specialised equipment in an appropriate setting. However, this process is time-consuming and well recognized as a problematic area in diagnostic surveys of institutions for the blind. This aspect is further discussed in subsection 11.6.1.

iii) An accurate history provides vital information, but is often lacking or fragmentary. Response to questionnaires is often poor even after repeated requests.

iv) Biological investigations (screening of urine for albumin, mucopolysaccharides, aminoacidurias, serum rubella antibodies) are not generally productive (Fraser and Friedmann, 1967). Karyotyping should be selective.

v) With regard to institutional surveys, the children present in a school for the blind represent a biased sample. Although many genetic causes for visual handicap will be encountered, those aetiologies causing multiple handicap, any conditions lethal in early childhood and late onset blindness will be incompletely represented.

9.4 NOSOLOGY OF INHERITED BLINDNESS

Blindness can be classified in various ways according to the investigator's leanings. Ophthalmologists often employ an anatomical approach while classification according to pathology or severity of visual disability is also favoured. In the present study where inherited causes received emphasis, visually handicapped persons were categorised as follows:

1. **Blindness as a recognized syndromic component:**
   Cases of blindness with co-existing dysmorphology or stigmata previously recognized or reported as syndromic concomitants were included.

2. **Undifferentiated familial blindness:**
   Blind individuals with non-specific ocular findings and no additional syndromic stigmata for whom close parental consanguinity (first or second cousins) was demonstrated, or the presence of two or more blind members of a family fitted a pattern of Mendelian inheritance, were included in this category.

3. **Blindness from well-defined acquired causes:**
   Post-natally acquired blindness from clear-cut environmental factors was readily classified under this category. Congenital eye pathology, however, presents a problem when attempting to differentiate between acquired causes and those of genetic origin. In the absence of clear historical or clinical evidence that incriminated acquired factors, blind individual's were assigned to category 4.

4. **Congenital blindness of poorly defined aetiology**

Congenitally blind individuals with non-contributory family histories, non-specific ophthalmological findings and absent or diagnostically unhelpful concomitant findings were classified within this group.

CHAPTER TEN

RESULTS OF AN AETIOLOGICAL SURVEY OF 84 BLIND INDIVIDUALS

10.1 INTRODUCTION

A total of 84 blind individuals were assessed. Sixty-two attended the *Lois Largesse Centre* and 22 were either individually referred or encountered during family studies. Fifty-three (64%) were males and 30 (36%) were female. A breakdown for ethnic origin is shown in Table 10-I.

ETHNIC GROUP	TOTAL	%
Hindu	36	43
Creole	22	26
Muslim	14	16,5
Franco-Mauritian	6	7
Chinese	2	2,5
Uncertain	4	5
TOTAL	**84**	**100**

Table 10-I: Ethnic origins of 84 blind individuals.

10.2 MAJOR CATEGORIES OF BLINDNESS

Totals for the major categories of blindness are presented in Table 10-II, on a basis of the classification outlined in paragraph 9.4.

	TOTAL	%
Undifferentiated familial blindness	14	16,7%
Blindness as a recognized syndromic component	16	19%
Blindness from well-defined acquired causes	26	31%
Congenital blindness of poorly defined aetiology	28	33,3%
TOTAL	**84**	**100%**

Table 10-II: Categories of blindness: percentage totals for 84 blind individuals.

10.3 BLINDNESS AS A RECOGNIZED SYNDROMIC COMPONENT

The 16 individuals with blindness as part of a recognized syndrome are listed in Table 10-III. This is followed by a brief case report of the Behr syndrome, Cockayne syndrome and Laurence-Moon-Biedl syndrome. The provisionally private syndrome (PPS # 3) is described and discussed in Chapter 15.

SYNDROME	MODE OF INHERITANCE	ADDITIONAL HANDICAP	TOTAL
Behr	AR	PH, MH	2 siblings
Cockayne	AR	MH, PH	1
Laurence-Moon-Biedl	AR	MH	1
Fronto-nasal Dysplasia	AD	-	1
Retinitis Pigmentosa (RP)	?	-	1
RP and Scoliosis	?	PH	1
Retinoblastoma	AD	-	6 family
Rieger Anomaly	?	-	1
Provisionally Private Syndrome # 3 (See Chap 15)	AR	Deaf, PH, MH	2 siblings
TOTAL			16

Table 10-III: Syndromic blindness in 16 individuals.

[MH = Mental handicap, PH = Physical handicap.]

10.3.1 Behr Syndrome (Optic atrophy with spasticity)

A brother and sister of Creole stock and non-consanguineous parents were examined at the respective ages of 21 and 16 years. They both presented with defective vision due to optic atrophy and rotational nystagmus and they had upper motor neurone signs in all four limbs, more marked in the legs. The present stable state was reached after a one year period of regression occurring in late infancy. Intelligence was difficult to assess owing to the visual problems and indistinct speech. These features were considered in keeping with the Behr syndrome (Horoupian et al, 1979).

10.3.2 Cockayne Syndrome

A boy, aged 3 years, was the only child of Muslim first cousins. His parameters at birth included weight: 1,5 kg; length 45 cm and a head circumference of 21 cm. His psychomotor development was globally retarded and he was beginning to walk unaided and say single words by the age of 3 years. On examination he had sunken eyes, a beaked nose, large ears and microcephaly. His limbs were disproportionately long and he had flexion contractures of the knees and elbows (Fig. 10-1). A photosensitive dermatitis which had a butterfly distribution on the face during the first year of life with recent extention onto the ear lobes. He had bilateral cataracts. (Fig. 10-2). The diagnosis of Cockayne syndrome was subsequently confirmed by Dr RJ Gorlin of Minnesota, USA.

Fig. 10-1: Cockayne syndrome showing disproportionately long limbs with flexion deformities of the knees and elbows.

Fig. 10-2: Cockayne syndrome: The facial features, skin changes and cataracts are evident.

10.3.3 Laurence-Moon Biedl Syndrome

A Hindu girl, aged 10 years, presented with deteriorating vision. Ophthalmological examination demonstrated retinitis pigmentosa. The concomitant features of mild mental retardation, obesity and polydactyly (Fig. 10-3) confirmed the diagnosis of the Laurence-Moon-Biedl syndrome.

Fig. 10-3: Laurence-Moon-Biedl syndrome in a girl aged 10 years.

10.4 UNDIFFERENTIATED FAMILIAL BLINDNESS

AR inheritance was implicated in 12 of a total of 14 cases of undifferentiated familial blindness, with parental consanguinity present in 7 instances. A single family with an affected uncle and nephew was considered in keeping with XL transmission. No families with undifferentiated AD blindness were found. This information is summarised in Table 10-IV.

INHERITANCE	MUSLIM	HINDU	GENERAL POPULATION	TOTAL
AR	5 (5)	5 (2)	2	12
XL	-	2	-	2
TOTAL	**5**	**7**	**2**	**14**

Table 10-IV: An analysis of undifferentiated familial blindness; figures in brackets represent the number of offspring from consanguineous marriages.

10.5 ACQUIRED BLINDNESS

An acquired aetiology accounted for blindness in 26 persons (31%) in this survey. A breakdown of these causes is presented in Table 10-V.

CAUSES	TOTAL
Prenatal and Perinatal	
Retrolental Fibroplasia	2
Rubella with deafness and mental handicap	2
Blindness with athetoid cerebral palsy	1
Blindness with quadriplegia	1
Ophthalmia neonatorum	1
Post-Natal	
Industrial or agricultural trauma	5
Severe systemic illness	4
Eye infections	2
Meningitis with mild mental retardation	2
Childhood accidents	2
Hypertensive retinopathy	1
Optic Neuritis	1
Unknown incident	2

Table 10-V: Aetiologies in 26 cases of acquired blindness

10.6 CONGENITAL BLINDNESS OF POORLY DEFINED AETIOLOGY

The major clinical findings in the 28 Mauritian individuals with congenital blindness of poorly defined aetiology are itemised alphabetically in Table 10-VI.

MAJOR CLINICAL FINDINGS	TOTAL
Anophthalmia	1
Blindness and hydrocephaly	1
Blindness and microcephaly	1
Blindness with cleft lip and palate	1
Cataracts	5
Colobomata (bilateral)	2
Corneal clouding	2
Glaucoma	2
Microcornea	3
Optic atrophy	2
Retinal detachment (bilateral)	1
Sclerocornea	2
Post-surgical obfuscation (including bilateral enucleations)	5

Table 10-VI: Congenital blindness of poorly defined aetiology.

10.7 ADDITIONAL STATISTICS

At the time of the survey, two additional sources of statistical information were obtained and are mentioned here, not because they are reliable for research purposes but to provide in the discussion that follows a perspective for the problem of blindness as a handicapping disorder on Mauritius:

i) Four hundred and forty-nine individuals are registered as blind for the purposes of social welfare.

ii) In an unpublished anonymous pilot survey towards a national programme for blindness on Mauritius, 1908 consecutive patients attending the Moka Eye Hospital from the 17th February 1976 to March 1986 were assessed. Fifty-three patients (2,8%) had a visual acuity less than 6/60 (Snellen). Eighty-nine percent (47) had senile cataracts (the commonest cause of blindness); the remaining 11% had a range of pathologies affecting both the anterior and posterior segments of the eye.

CHAPTER ELEVEN

BLINDNESS ON THE ISLAND OF MAURITIUS: DISCUSSION

11.1 INTRODUCTION

The incidence of blindness on Mauritius is unknown and prior to the present survey there has been no investigation into genetic disease and visual handicap. Personal communication with local ophthalmologists regarding eye disease in general indicated a predominance of posterior segment pathology. It is generally accepted that abnormalities of this type (diabetic retinopathy, optic atrophy, macular degeneration) have their highest incidence in the developed world while third world communities tend to have a predominance of anterior segment pathology (corneal scars, infections, trauma).

Mauritius, a developing country, has a distribution of eye pathology which is usually encountered in the first world. Both environmenntal and genetic factors play a role in this paradoxical situation. This island community has largely escaped certain endemic infections like trachoma and onchocerciasis which are still common causes of blindness in the African and Asian continents; vitamin A malnutrition, common in the third world, is rare in the fishing populations of an oceanic island. However, the Indo-Mauritians have a high incidence of hypertension and diabetes mellitus; both these diseases have significant ocular sequaelae and complex genetic factors in their aetiology.

Thirty individuals representing 35,7% of the persons in this study were blind as a result of genetic disease; 19% represented recognizable blindness syndromes and 16,7% fell within the familial undifferentiated category. The incidence of inherited blindness could be considerably higher as additional cases are almost certainly present within the group of 'unknown' aetiology.

In this chapter, the results of the Mauritian survey are analysed by aetiological category and problems pertaining to a study of this nature are discussed.

11.2 BLINDNESS AS A RECOGNIZED SYNDROMIC COMPONENT

Blindness is a concomitant feature to many syndromes. Frequently, in addition to the visual disability, other handicaps and developmental problems are present and their severity may preclude admission to institutions for the blind. Surveys may thus fail to ascertain such conditions.

The majority of the 16 individuals categorised in this group were obtained through individual referrals. Although additional handicapping disorders have been listed (Table 10-III), therapists responsible for the individual's care, considered the visual handicap in these cases to be the greatest obstacle to rehabilitation.

In this category, an accurate diagnosis is central to effective management and counselling. Points of discussion arising from some of the recognized syndromic causes of blindness are considered below.

11.2.1 Cockayne Syndrome

The classical characteristic features of this rare AR syndrome were present in the child portrayed in Fig. 10-1 and Fig. 10-2 and included: a typical birdlike facial appearance, cataracts, disproportionately long limbs with flexion deformities, psychomotor retardation and the photosensitive skin rash with sparse coarse hair (Houston et al, 1982; Moyer et al, 1982).

Rare AR conditions like Cockayne syndrome can be expected from consanguinous unions in isolated communities and the correct diagnosis may be missed. The help of the computerised birth defects information centre (BDIS) proved useful in expanding the differential diagnosis, but consultation with colleagues with special experience provided the most valuable assistance in reacting an accurate diagnosis.

11.2.2 Laurence-Moon-Biedl Syndrome (Current nosology considers the Bardet-Biedl syndrome more accurate)

The finding of retinitis pigmentosa, obesity, mild mental retardation and polydactyly in a Hindu girl, confirmed the diagnosis of the Laurence-Moon-Biedl syndrome. As the disorder is transmitted as an AR trait, it is possible that this faulty gene is present in additional members of the Hindu community.

Until recently, this girl's mental handicap received greater priority regarding rehabilitation and specialised education (she is also mentioned in the section on genetic disease and mental handicap - chapter 13). However, the development of blindness as part of the natural history for this disorder, will demand a shifting of emphasis in her institutional care. The accurate diagnosis in this situation facilitates the prediction of impending problems and thus assists in the planning of appropriate management. Equally, an accurate genetic diagnosis affords accurate counselling of recurrence risks.

11.2.3 Retinitis Pigmentosa (RP)

RP is a heterogeneous disorder with multiple forms of inheritance and several syndromic associations (Allard, 1983). It is probably the most common form of genetic blindness with an incidence of 1/3700 in the USA (Boughman et al, 1980). The 3 cases which were detected in this survey, almost certainly are an under-estimation of the real prevalence on Mauritius. Special expertise and sophisticated investigations are required to detect the milder autosomal dominant form or to diagnose RP in its early stages. Advanced cases are often masked by cataract and myopia.

The scoliosis which was present in one individual is not a known syndromic concomitant; no other family members were similarly affected.

11.2.4 Retinoblastoma

Six cases of retinoblastoma were found in a large Franco-Mauritian family (Fig. 11-1). Recent research has shown that in the heritable form of retinoblastoma, a point mutation or deletion is present on one chromosome 13 in all cells. A so-called 'double-hit' results in conversion to the homozygous state in the developing retina (Cavenee et al, 1983).

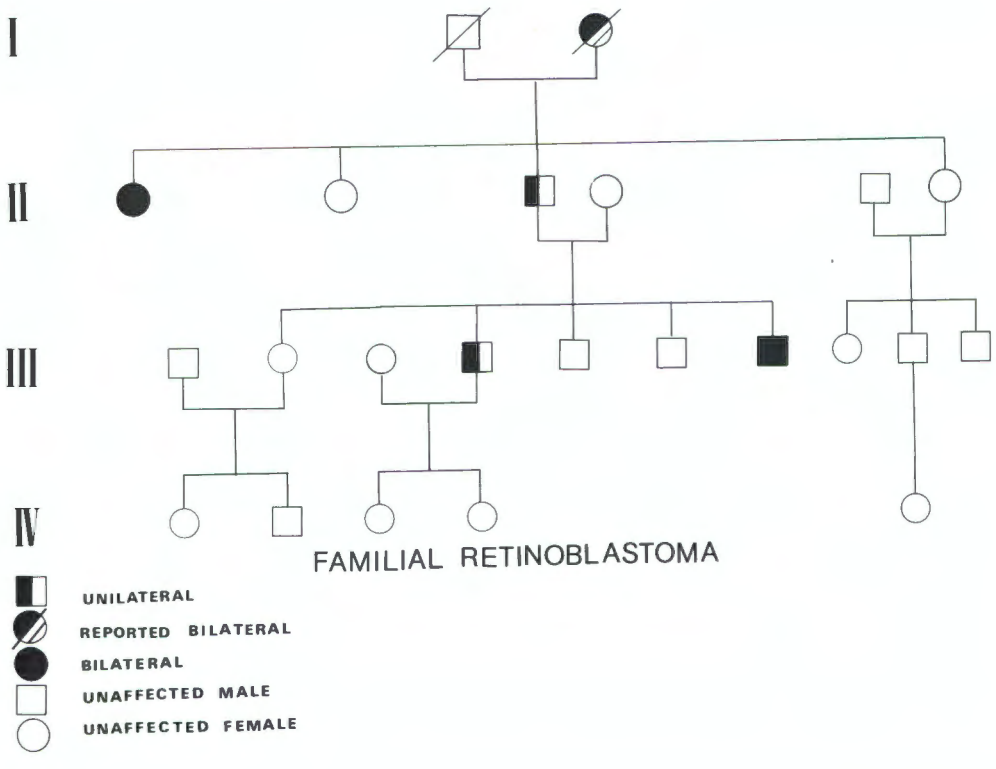

Fig. 11-1: A genealogical representation of AD retinoblastoma.

Identification of individuals with retinoblastoma is thus of great importance for follow-up of the unaffected eye and long term observation of the offspring, even in unaffected family members (Atherne and Roberts, 1975). The estimation of

esterase D levels (Cowell et al, 1986) and the detection of a small sub-band deletion (Cowell et al, 1987) will lead to diagnostic DNA probing within the near future.

The Mauritian family will benefit greatly from these advances. A blood sample, easily transported to an appropriate centre, if found to be negative will assuage emotional stress and circumvent the need for bi-annual travel to major centres. Positive results for the test will facilitate the planning of early intervention and management. In the appropriate clinical setting, laboratories, functioning at the forefront of medical science can thus, with immediate effect, assist developing communities. However, an accurate genealogical documentation by local personnel is a prerequisite if these cost-effective services are to be implemented.

11.3 UNDIFFERENTIATED FAMILIAL BLINDNESS

Almost 17% of the blind individuals documented in this survey were classified as having undifferentiated familial blindness. This total approximates the figure of 21% recorded by Fraser and Friedman (1967). The absence of any families with AD undifferentiated blindness is probably due to a negative founder effect and is further discussed in paragraph 11.7.

The difficulty in differentiating between AR and XL patterns of inheritance in some families, parallels the problem encountered with deafness (paragraph 8.3). All the Muslim individuals with undifferentiated blindness had consanguineous parents and the role of intra-familial marriage as an aetiological factor is emphasised.

It is of interest that the Muslim community, as a population group, is numerically smaller than the Hindu Mauritian by a ratio of approximately 1:3,5. However, AR blindness is represented equally in both groups and possibly reflects the tendency toward consanguinity in the former.

11.4 ACQUIRED BLINDNESS

The Mauritian survey incriminated acquired factors in 31% of the blind individuals assessed. As the School for the Blind caters predominantly for the rehabilitation and education of the visually handicapped individual, preference is given to children. Commonly encountered acquired causes of blindness, affecting the adults on Mauritius (hypertensive retinopathy, diabetic retinopathy, senile cataract) were therefore not investigated. In addition, any condition resulting in monocular visual loss was excluded from the survey.

Industrial or agricultural trauma was commonly implicated as an aetiological factor (19%) and underlines the need for adequate safety and protection in these activities.

In a study of 776 visually handicapped children in the United Kingdom, Fraser and Friedman (1967) documented acquired causes in 50% of cases. Common aetiologies included; retrolental fibroplasia (23%); rubella (3%); optic atrophy following meningitis or tumours (4%) and perinatally acquired cataract (4%).

Maternal rubella as a cause of prenatal blindness, warrants review in the light of recent reports. Munro et al (1987) investigated the temporal relations between maternal rubella infection in pregnancy and the presence and type of defect in 422 children with confirmed congenital rubella. In this series, no foetal defects were recorded if maternal infection

occurred after the 17th week; conversely, no foetus escaped damage if infected before 7 weeks of intra-uterine life.

These authors noted, that when eye defects were present, (5 with cataracts, 8 with retinopathy, 1 with bilateral glaucoma), all infections occured within the 1st trimester. In addition, none of these 14 children had isolated ocular sequalae. Mental retardation was a common concomitant and deafness occurred in all but one individual. This observation has considerable bearing on diagnostic surveys. Admission to schools for the blind generally impose restrictions on additional handicapping disorders; the ability to hear is usually an essential criterion for admission. Thus, it could be expected that aetiological surveys of institutions for the education of the blind are unlikely to encounter rubella-related eye pathology. No cases of confirmed rubella were found at the Mauritian Institute for the Blind. The two individuals listed in Table 10-V were referred by local practitioners. Both were ineducable due to co-existing mental retardation and deafness.

11.5 CONGENITAL BLINDNESS OF POORLY DEFINED AETIOLOGY

Twenty-eight congenitally blind individuals with non-contributory family histories had non-specific findings on ophthalmological examination. In addition, concomitant findings on general examination were absent or diagnostically unhelpful. These sporadic cases could represent recessive genetic entities or new dominant mutations. In addition, unknown pre- and perinatally acquired factors are almost certainly included in this category.

Bilateral congenital cataracts were the commonest clinical finding for this group, in keeping with similar studies (Merin and Crawford, 1971; Keith, 1974). The contribution of genetic factors is thought to be between 25% (Merin and Crawford - 386 cases) and 51% (Keith - 55 cases). For the lens, cataract formation is the end-response to a wide range of insults or embarrassments. Distinguishing the metabolic abnormalities causing lens opacities from those due to gene defects or congenital infections presents considerable clinical difficulty and partly explains the discrepancies found in the above studies.

Research and improved screening techniques are required to further clarify the underlying aetiologies in this category of congenital blindness. Until such time, genetic counselling for these sporadic cases remains difficult and, at best, must be guarded.

11.6 AETIOLOGICAL SURVEYS OF THE BLIND: PROBLEMS ENCOUNTERED

11.6.1 Examination of the Eye

Systematic study of an affected individual at the time of first diagnosis of the visual handicap would provide optimal aetiological data. Institutional surveys are, however, essentially retrospective. The ocular changes observed may reflect acquired secondary changes and the underlying aetiology is masked with the passage of time. An example of this difficulty is portrayed in Fig. 11-2. This adolescent female was blind since birth with no additional dysmorphic features or affected relatives. Her ophthalmological findings include glaucoma, sclerocornea, and micro-ophthalmia. Surgical intervention to remove a cataract had further obscured the clinical picture.

The eye has only a limited number of clinico-pathological reactions to a wide range of biological insults, be they acquired or genetic. Cataracts, for example, may be inherited or acquired, and distinguished clinically with difficulty and dubious accuracy, even by experts. Conversely the same aetiological agent may lead to pathological end-points which are generally ascribed to different diagnostic categories. For example, sclerocornea and Peters anomaly can be manifestations of a single gene (Salmon et al, 1988).

In the absence of histological clues and biochemical markers for the cause of an ocular anomaly, the accurate delineation of inherited blindness, in the future, may lie in the realm of biology.

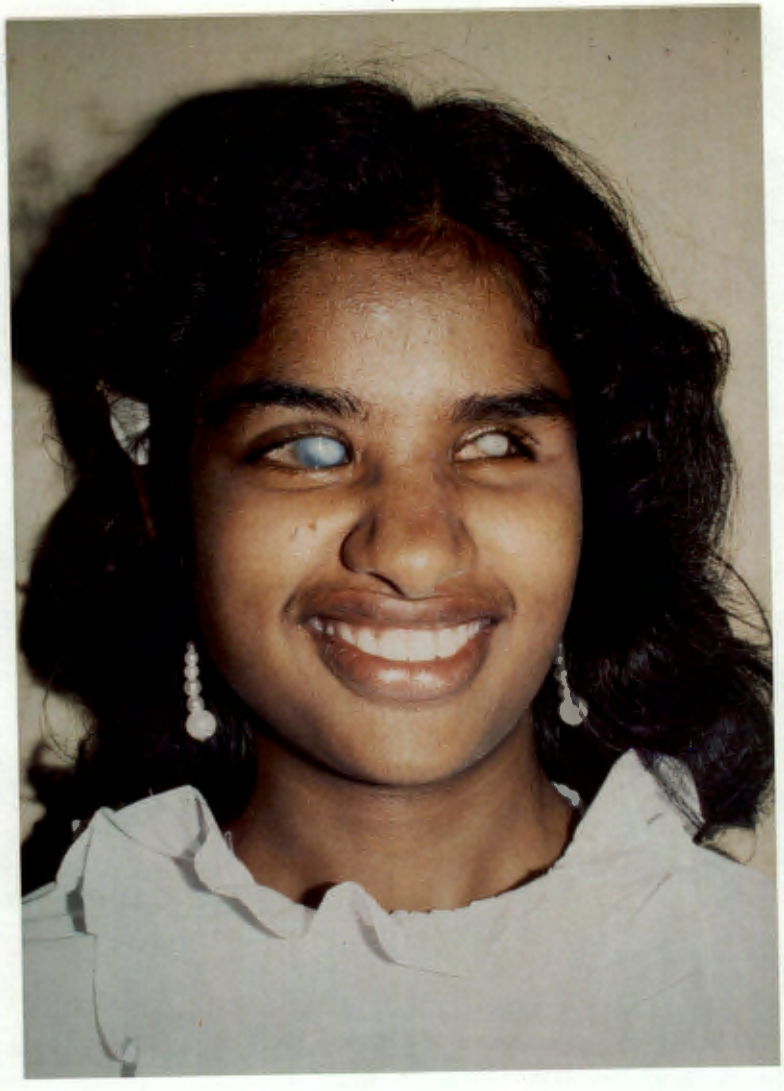

Fig. 11-2: Secondary ocular changes mask the underlying aetiology in this blind girl.

11.6.2 Inadequate Anamnestic Data

Retrospection enforces a dependance on records and a past history. These are often incomplete, fragmentary or unavailable. Attempts at overcoming this problem on Mauritius were approached in two ways. A questionnaire designed in co-operation with a local specialised teacher, was sent to the parents of affected children, requesting family details, the natural history of the individual's visual disability and other pertinent information. The response was poor, for reasons unclear, and further attempts were abandoned.

Information retrieval from hospital records was equally unsuccessful. Problems included the alteration of the spelling of names with time, birthdate shift, destroyed files and death of doctors with illegible handwriting!

11.7 FINAL COMMENT

The presence of genetic blindness on the Island of Mauritius has been documented in this section. It is evident that an awareness of the role of genetic disease is vital if accurate diagnosis, management and counselling is to be rendered.

Two observations remain and deserve mention. In this survey there was a preponderance of males (64%) to females (36%). X-linked inheritance might explain this discrepancy but an ascertainment bias is probably responsible. The blind male, in most sections of Mauritian culture, is less likely to be of use in the home and is therefore encouraged to attend the Centre for the Blind to acquire a remunerative skill or trade. A blind girl or young woman, is accepted at home, and might thus escape ascertainment in an institutional survey.

The low prevalence of blindness with AD inheritance for this survey is in contrast to other reports (20% in 776 children; Fraser and Friedman, 1967). Possibly, blind individuals are negatively selected against in the process of emigration to a new and isolated community, especially if the environment is foreign in structure and lacking in facilities. With this negative founder effect, only spontaneous dominant mutations would have the potential for initiating a dynasty of AD blindness. If such a mutation should occur on Mauritius, it is feasible that the resulting handicap might preclude marriage and procreation, especially if the host community is small and further restricted by socio-religous boundaries. These questions, as with many pertaining to inherited blindness, remain unanswered and await further study.

SECTION V

GENETIC DISEASE AND MENTAL RETARDATION

ON MAURITIUS

In this section the role of genetic disease as an aetiological factor in mental retardation on the Island of Mauritius is reviewed under the following Chapter headings:

CHAPTER 12

GENETIC DISEASE AND MENTAL RETARDATION

12.1 INTRODUCTION

The causes of mental handicap are diverse and span the full spectrum of inherited and environmental aetiologies. In addition to the purely genetic entities or clear-cut environmental causes, there is an inevitable "grey zone". Here, factors from both categories contribute to the mental disability; the foetal alcohol syndrome is an example of this large and complex area.

Considerable progress has been made in recent decades towards the diagnostic categorisation of mental retardation (Thoene et al, 1981). This process has been facilitated by improved cytogenetic techniques, a better understanding of molecular biology and the development of sophisticated radiological facilities. For these reasons, however, the thorough investigation of a child with mental retardation is becoming increasingly extensive, invasive and expensive.

In many developing communities, sophisticated diagnostic technology is not available. Indeed, investigations of this nature might be considered economically inappropriate. In this milieu, institutionalisation frequently signals the end of diagnostic effort; health care workers, administrators and educationalists have only a broad and frequently meaningless aetiological label for the affected individual. Parents are

unaware of the diagnosis, the prognosis or subsequent risks to the family and may unnecessarily cease reproduction or suffer the tragedy of further affected offspring.

In this Chapter, the use of certain terminology and the criteria for an aetiological survey into mental retardation on Mauritius are defined and an appropriate and practical classification is presented.

12.2 MENTAL RETARDATION : GENERAL BACKGROUND

12.2.1 Incidence

The population prevalence for significant mental retardation (IQ < 50) in Western Europe and North America is approximately 4 per 1000, a figure derived from the results of surveys performed in a number of centres (Penrose, 1966; Milunsky, 1975; Costeff and Weller, 1987). The cause for the mental retardation is generally unknown in almost 40% of cases.

The incidence of genetic disease in institutionalised mental retardates lies between 20 - 45% (Opitz et al, 1978). Discrepancies between various studies can be explained by the differences in ascertainment criteria and the definitions of mental retardation which are used.

12.2.2 Definitions

Mental handicap may be defined in educational, psychological and sociological parlance as well as in medical terms. Attempts at a single classification have met with little success; for example, teachers need a format that will lead to appropriate classroom goals, administrators must plan resources, and employers require knowledge of potential ability. For the physician and clinical geneticist, information concerning aetiological factors which are responsible for the mental retardation are of prime importance in management, prevention and counselling.

12.2.3 Intelligence Testing

The criteria adopted in defining a mentally handicapped population are ultimately arbitrary. Intelligence Quotient (IQ) testing using a recognized format (Stanford-Binet and Cattel tests) is widely accepted. There are obvious limitations of such tests, notably cultural factors.

Most surveys have involved populations of retardates with an IQ below a score of 50. This includes the profound (< 20), severe (20-35) and moderate range (35-50), as persons in all three categories are generally institutionalised together (Penrose, 1966).

Recently, interest has been focused on mildly retarded individuals with an IQ in the range 50-70. These children are generally identified as poor school performers and are streamed into remedial classes during the first few years of formal education. Ultimately, they may integrate satisfactorily into social and vocational endeavours. Adverse socio-economic factors, in addition to the expected variability of human intelligence, are significant causative factors in mild retardation (Stein and Susser, 1969). Individuals with an IQ < 50 might thus be recognised as a second group in whom the prevalence of pathological conditions increases as the IQ decreases.

12.3 SURVEYS INTO MENTAL RETARDATION

Surveys of mentally retarded communities can be divided into four broad categories: those concerned with prevalence rather than cause (Kushlik, 1966), aetiological surveys based on data from institutions (Fryns et al, 1986), studies confined to strictly defined age groups (McDonald, 1973) and investigations of mental handicap within special geographical boundaries (Laxova et al, 1977).

The aims of diagnostic surveys vary according to their structure, however, certain central principles are common to all:

(i) The classification of a large body of data into simple yet informative categories is of special use in understanding the causes of mental handicap in the sampled group.

(ii) The identification of common causes gives an indication to health care planners of pathological processes which warrant special attention or intervention.

(iii) Based on the results of an initial screening survey, the further investigation of individuals with mental retardation can be modulated to be most cost-effective and least invasive.

12.4 AN AETIOLOGICAL CLASSIFICATION FOR MENTAL RETARDATION

12.4.1 Introduction

There is no flawless aetiological classification for mental handicap. Ideally, the structure must be applicable to the clinical setting. In a developing country, facilities for specialised investigations are frequently unavailable, but these constraints should not detract from the success of a survey. Individuals with mental retardation due to undefined causes can be broadly categorised until such time as new expertise and improved technology permit differentiation. This approach facilitates analysis, assists with counselling and affords easier case retrieval for re-evaluation in the face of advancing knowledge.

The following classification was designed for the Mauritian survey with the aforementioned points in mind. The categories are briefly presented here to facilitate the interpretation of the results given in Chapter 13. In Chapter 14, further explanation and expansion is expounded.

12.4.2 The Classification

A) **Syndromic mental retardation:**

Disorders with mental retardation plus additional clinical stigmata are further sub-divided into:

i) Chromosomal disorders

ii) Mendelian inheritance

iii) Malformation syndromes

B) **Central nervous system (CNS) malformations:**

This category comprises individuals who are morphologically normal but in whom special investigations have revealed a structural CNS abnormality. They can be subdivided into two groups:

i) Sporadic

ii) Familial

C) **Cerebral palsy and/or epilepsy group:**

This group includes children with a marked neurological deficit, most likely of perinatal onset and often suspected prior to documentation of the mental retardation. In these children, there are no additional congenital abnormalities, no CNS malformations, no history of post-natally acquired conditions and no genealogical evidence of Mendelian inheritance. Individuals with well controlled fits and without additional neurological signs are not included in this category.

D) **Acquired aetiology:**

Persons with mental retardation resulting from a well documented environmental cause are included in this group.

E) **Undiagnosable mental retardation:**

This diagnosis is made by exclusion. These patients do not fit into the previous categories and can be allocated to one of three subgroups:

i) MR without additional dysmorphism
   - sporadic
   - familial

ii) MR with additional dysmorphism
   - sporadic
   - familial

iii) MR with autistic manifestations
   - sporadic
   - familial

CHAPTER 13

A DIAGNOSTIC SURVEY OF 307 MENTALLY RETARDED INDIVIDUALS ON MAURITIUS: AIMS, METHODS AND RESULTS

13.1 INTRODUCTION

The aims of this study were:

(i) To establish minimum prevalence figures for different categories of mental retardation on Mauritius;

(ii) To assess the contribution of genetic disease to mentally handicapping disorders;

(iii) To identify and document unusual and possibly unique genetic entities;

(iv) To provide a classification of mental retardation disorders that is valid, functional and informative for the Island; and

(v) To provide the basis for accurate counselling and management.

Initially, the survey set out to document only those persons with an IQ < 50. Two factors, however, stimulated an interest in the mildly mentally handicapped group (IQ 50-70). Firstly, while assessing non-institutionalised patients with intelligence in the mildly retarded range, a number of genetic entities were encountered. Secondly, the special educational needs for the children in the range of IQ: 50-70, are catered for by a single large institution on Mauritius (see paragraph 13.3.2). Using these facilities, a systematic study could be made of a numerically significant sample of mildly retarded children. For these reasons, two separate groups of mentally handicapped individuals were assessed.

Of the total of 307 individuals, 196 were in the category of mental handicap with an IQ < 50 and 111 were mildly retarded. These two groups have been documented and analysed separately in keeping with traditional concepts (see paragraph 12.2), thus facilitating comparison with previous studies. In this chapter, the methods used in assessing the mentally retarded individuals on the Island of Mauritius are summarised and the results of the survey are presented.

13.2 CLINICAL METHODS AND SPECIAL INVESTIGATIONS

13.2.1 Clinical Methods

The survey was primarily based on a clinical and genealogical approach. A standardised proforma outlining essential questions and physical findings was used for all patients (see Appendix A). These forms allowed easy entry into a computer-data system to provide analysis of epidemiological, clinical and genetic characteristics. A careful physical examination was performed and dysmorphic and abnormal neurological findings were especially sought. Genealogical information was gleaned from the acquisition of comprehensive family histories.

13.2.2 IQ Assessment

The terminology describing various IQ ranges is controversial. For the purposes of this thesis, severe mental retardation (SMR) refers to all individuals with an IQ less than 50 and embraces the terms 'moderate', 'profound', 'trainable' and 'dependent' (Grossman, 1977). Mild mental retardation (MMR) includes persons with an IQ: 50-70, sometimes referred to as 'educable'.

The IQ of many of the individuals in this survey had previously been assessed by local professionals using standard scales. If such information was unavailable, the severely retarded individuals (IQ < 50) generally presented little problem in clinical identification and categorisation, using behaviourial criteria. In the case of children unable

intellectually to attend school but not severely retarded, educability and the potential for social independence were the broad criteria that permitted allocation to the 50-70 range.

13.2.3 Special Investigations

Limited facilities were available on Mauritius for special investigations. In selected individuals, where sophisticated testing was considered beneficial in the formulation of a precise aetiological diagnosis, the following investigations could be obtained:-

i) **Conventional radiography.**

No facilities for ultrasound evaluation, computerised tomography or magnetic resonance imaging were available.

ii) **Chromosomal analysis.**

By special arrangement, blood specimens were sent for karyotyping to the Department of Human Genetics, University of Cape Town, and the Blood Transfusion Services, Durban. Difficulties with transportation and cost-factors limited the investigation to 15 individuals. These cases were carefully selected and the results are presented at the end of this chapter. The protocol for culture and karyotyping is presented in Appendix C.

iii) **Biochemical investigations.**

Baseline biochemical investigations, including serum uric acid estimations, could be undertaken on Mauritius. Special mention must be made of the inborn errors of metabolism. The survey was never intended to comprehensively investigate or document this group of disorders as the logistical requirements were well beyond the available facilities. However, in a few cases of metabolic MR, a diagnosis had been established

at an overseas centre and the results are incorporated in this section.

iv) **Previous investigations.**

Before the survey, certain individuals had used private means in order to travel overseas for special investigations. (TORCH screening, tests for phenylketonuria, CT scan, EEG). This information, when available, was utilised.

13.3 SOURCES OF SAMPLE ASCERTAINMENT

13.3.1 Association de Parents d'Enfants Inadaptès de l'Ile Maurice (APEIM)

APEIM is an association that provides a service to the parents and families of mentally handicapped persons on Mauritius (Fig. 13-1). In addition to the promotion of welfare and understanding for these individuals, with programmes to arouse and sustain public interest, APEIM runs schools for the education and training of mentally retarded children. Established in 1970 by a group of parents, the association has grown in structure and stature and has achieved a high measure of public esteem and trust. Local medical practitioners and specialists readily refer affected patients to the centre and utilize the services. Parental education is slowly removing the stigma attached to mental handicap that prevails in some sectors of the community. To date, some 2000 affected individuals are documented in the APEIM records.

106 children and adolescents attending the day school, playgroups and vocational training units were assessed. In addition 82 newly diagnosed children referred for assessment and placement to the unit over the 3 month study period, were included in the findings. Local doctors, aware of the survey through hospital lectures, referred patients suspected of having a genetic cause for their mental handicap (12 cases) and four individuals were brought by their families following a press report (see Appendix D).

From these sources, and with the outstanding co-operation of the dedicated staff at APEIM, 203 children and adolescents representing all cultures and socio-economic groups, were ascertained, examined and counselled. Of these patients, 193 were classified within the category of severe mental retardation.

Fig. 13-1: The staff of the Association de Parents d'Enfants Inadaptès de l'Ile Maurice.

13.3.2 The School for the Education of the Sub-Normal (ESN)

This institution caters for children of school-going age who are intellectually incapable of progressing within the normal educational system but who were educable. The IQ range of the majority of pupils falls within the range 55-70. It is the only school on Mauritius that specifically accommodates this group of children thereby catering for a wide range of individuals, both socially and geographically. 69 children from ESN were available for examination and represented approximately 60% of the school's enrolment.

13.3.3 Other Institutions

As alluded to previously (paragraph 11.4) mental retardation can be associated with additional handicapping pathology.

During surveys of institutions for the blind, deaf and physically handicapped, a number of individuals with mild mental retardation (IQ: 50-70) were detected. In 32 instances the mental handicap was considered to be of special significance and these persons have therefore been incorporated within the statistics of this chapter.

13.3.4 Additional Comment

No individuals with a primary psychiatric illness were included in the Mauritian survey although mention is made of children with autism. Thus, the inclusion of 3 patients with Huntington disease into the statistics for severe mental handicap is clearly debatable. However, as the disease has considerable historical and genealogical implications for the Island, incorporation is warranted. A full discussion is provided in the chapter on genetic diseases of special significance to Mauritius (Chapter 22).

13.4 RESULTS

13.4.1 Diagnostic Groups and Subgroups

In Table 13-I the totals for each of the diagnostic groups is shown. In the subsequent Tables, further analysis is presented.

DIAGNOSTIC CATEGORY	SMR	MMR	TOTAL	%
Syndromic MR	71	14	85	27,5
CNS Malformations	4	0	4	1,5
CP and/or epilepsy	46	13	59	19
Acquired	22	8	30	10
Undiagnosable MR	53	76	129	42
TOTAL	**196**	**111**	**307**	**100**

Table 13-I: Major aetiological diagnostic groups for 307 mentally retarded individuals. (MR = mental retardation; SMR = severe mental retardation; MMR = mild mental retardation; CNS = central nervous system; CP = cerebral palsy.)

13.4.2 Known Syndromic Mental Retardation

SUBGROUP	SMR	MMR	TOTAL	%
Chromosomal			67	79,0%
Trisomy 21	54	10		
Prader-Willi syndrome	1	1		
15p+	1	-		
Mendelian			14	16,5%
AD: Huntington disease	3	-		
Tuberous sclerosis	2	-		
Hypochondroplasia*	-	1		
AR: Prader-Willi syndrome with albinism	1	-		
Alkaptonuria*	-	1		
Laurence-Moon-Biedl syndrome	-	1		
Phenylketonuria	1	-		
Tay-Sachs disease	1	-		
AR/XL: Hydrocephalus	2	-		
XL: Lesch-Nyhan syndrome	1	-		
Malformation Syndromes			2	2,5%
Epidermal naevus syndrome	1	-		
Rubinstein-Taybi syndrome	1	-		
Miscellaneous			2	2,0%
Cretinism	2	-		
TOTAL	71	14	85	100%

Table 13-II: Sub-categorization of 85 individuals with syndromic mental retardation. (* dual pathology probable)

13.4.3 CNS Malformations

CNS malformations were diagnosed in 4 sporadic individuals with severe mental retardation, at overseas centres. Three had congenital hydrocephalus and one had agenesis of the corpus callosum.

13.4.4 Cerebral Palsy and/or Epilepsy

A total of 59 individuals had cerebral palsy and/or epilepsy. Further analysis of these data is beyond the scope of this thesis except to differentiate those individuals with severe mental retardation (46 cases) from those with cerebral palsy and mild mental retardation (13 cases).

13.4.5 Acquired Aetiology

Thirty persons were mentally handicapped from well documented acquired causes. Nineteen children had suffered a serious illness (meningitis, encephalitis, high fever with recurrent convulsions, tetanus); of these 13 had SMR and 6 had MMR. Five children with prenatal infection (3 Rubella, 1 cytomegalovirus, 1 unknown) presented with SMR. Accidental head injuries caused MR in 3 children and there was one instance of SMR following accidental poisoning. The foetal alcohol syndrome was not observed and there were no suspected victims of childhood battering or drowning.

13.4.6 Undiagnosable Mental Retardation

129 individuals with MR were unclassifiable. In this analysis they have been grouped together according to the degree of mental handicap, the presence or absence of additional dysmorphic features and evidence for Mendelian inheritance (similarly affected family members, parental consanguinity, or both). This information is summarised in Table 13-III and Table 13-IV. A list of the dysmorphic features in these individuals is given in Table 13-5. Further description of persons with so-called 'provisionally private syndromes' (PPS) are presented in Chapter 15.

Without additional dysmorphism	**SMR**	**MMR**	**Total**
Sporadic	16	41	54
Familial	10	22	32
			86 (67%)
With additional dysmorphism	**SMR**	**MMR**	**Total**
Sporadic	13	9	22
Familial	10	4	14
			36 (28%)
With autism	**SMR**	**MMR**	**Total**
Sporadic	4	-	4
Familial	3	-	3
			7 (5%)

Table 13-III: An analysis of 129 individuals with undiagnosable mental retardation.

Familial Undiagnosable MR		
Without additional dysmorphism	**SMR**	**MMR**
With affected kin	6(3)	19(7)
With parental consanguinity	4(4)	1
Consanguinity and affected kin	-	2(1)
With additional dysmorphism	**SMR**	**MMR**
Affected kin	3 [PPS#1]	2(1)
With parental consanguinity	1 [PPS#2]	2(2)
Consanguinity and affected kin	6 [PPS#3,4,5]	-

Table 13-IV: An analysis of familial undiagnosable mental retardation. (Figures represent the total number of affected individuals. Figures in round brackets indicate the total number of families involved.)

[PPS = provisionally private syndrome: for a description consult the relevant entry in Chapter 15.

DYSMORPHISM	SMR	MMR
Cleft lip and palate [PPS # 6]	2	1
Triangular face, arachnodactyly [PPS # 7]	-	1
Dwarfism with coarse facies [PPS # 8]	1	-
Abnormalities to tip of nose, fifth fingers, palmar markings and ears [PPS # 9]	-	1
Marfanoid habitus (Fig 13-2)	-	2
Icthyosis	-	2
Frontal hair sweep (Fig 13-3)	1	-
Bilateral simian crease, normal karyotype	2	-
Blind and deaf	1	-
Deafness	2	1
Cafe-au-lait macules	1	1
Hypospadias and cafe-au-lait macules	1	-
Limited elbow extension	1	-

Table 13-V: Dysmorphic stigmata in sporadic individuals with undiagnosable mental retardation.

[PPS = provisionally private syndrome: See Chapter 15]

Fig. 13-2:

A Marfanoid habitus with wind-swept deformities of the knees in a mildly retarded male.

Fig. 13-3: A frontal hair sweep in a mentally retarded boy.

13.5 CONSANGUINITY

Close consanguinity (first or second generation cousins) was present in the parents of individuals with the following mentally handicapping conditions:

i) Alkaptonuria

ii) Cockayne syndrome (Fig. 10-2 and Fig. 10-2)

iii) Hydrocephalus

iv) Eleven families with undiagnosable mental retardation

Further differentiation according to ethnic group was not undertaken.

13.6 SEX DISTRIBUTION

There was no significant difference between the sexes in either the severely or mildly retarded groups. Of the 307 individuals, 147 were females and 160 were males.

13.7 CHROMOSOME ANALYSIS

Chromosomal analysis was performed on 15 individuals. As stated previously, logistical factors severely limited the taking and testing of samples. Candidates for karyotyping were carefully selected with priority given to individuals most likely to benefit from the results. The salient features that justified cytogenetic analysis and the karyotypic findings are listed here:-

1. *Male, aged 16 years. IQ < 50, no speech or dysmorphic features; normal genitalia; one of two brothers identically affected (Fig. 13-4).*

   ? Martin-Bell syndrome

   Result: 46,XY - no fragile sites detected.

Fig. 13-4: Brothers with undiagnosable mental retardation and normal karyotype.

2. *Male, aged 4 years. Globally retarded with frequent convulsions. Abnormal features included small stature, bilateral cleft lip, antimongoloid slant of the eyes, clinodactyly, polydactyly (PPS # 6; Fig. 15-2).*

Result: 46,XY

3. *Chinese girl aged 9 years. Deaf with poor scholastic progress. Brother deaf.*

? Trisomy 21.

Result: 46,XX

4. *Boy aged 12 years, poor school progress, single simian crease, proximally placed thumbs, clinodactyly, anterior hairline and synophrys. (Fig. 13-5; Fig. 13-6).*

? Cornelia de Lange syndrome

? Trisomy 21

Result: 47,XY + 21

5. *Chinese girl aged 15 years, sister of 2 brothers with global retardation and marked hyperactivity.*

? Fragile X

Result: 46,XX

6. *Male aged 18 years, tall stature, profound mental retardation, cleft palate, normal genitalia, previously diagnosed as XYY.*

Result: 46,XY

7. *Chinese girl aged 6 years, albinism and phenotypic features of the Prader-Willi syndrome; floppy at birth, required tube feeding for first 6 months, subsequently a voracious eater; obese, small hands and feet. (Fig. 14-7).*

Result: 46XX. Paracentric inversion of the no 9 chromosome (normal variant).

Fig. 13-5: Atypical facial features in a boy aged 12 years, with Down syndrome (karyotype # 4).

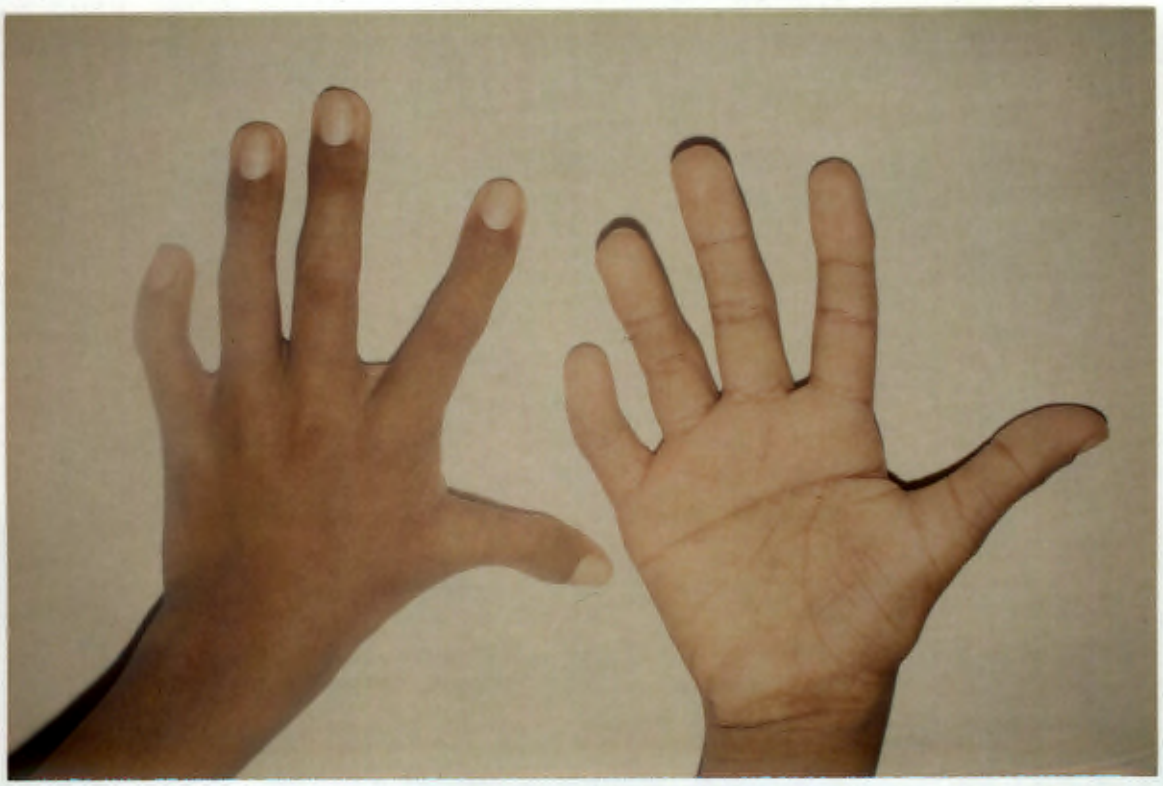

Fig. 13-6: The hands of the boy in Fig. 13-5: The posteriorly placed thumbs, clinodactyly and simian crease are evident.

8. *Male aged 20 years, one of three mentally retarded brothers with similar facies, tall, large ears, normal testes, sister of normal intelligence. ? Fragile X (PPS # 1; Fig. 15-1).*

Result: 46,XY - no fragile sites were detected.

9. *Female aged 20 years, delayed psychomotor development, outbreaks of violent temper, small hands and feet provisionally diagnosed as Prader-Willi syndrome.*

Result: 46,XX

10. *Boy aged 3 years, with a differential diagnosis that included Bloom syndrome. Subsequently confirmed as Cockayne syndrome. (Fig. 10-1 and Fig. 10-2).*

Result: 46,XY

11. *Girl aged 3 years, elder brother identically affected with severe global retardation, corneal clouding, large protruding ears, agenesis of corpus callosum, eczema, dolicocephaly. [PPS # 3]*

? Chromosomal deletion syndrome

Result: 46,XX

12. *Male, aged 24 years, with coarse facies, large ears, protruding tongue,large testes, profound mental retardation.*

? Fragile X

Result: 46,XY

13. *Male, aged 18 years of Chinese-Hindu origins with simian creases, mongoloid eyes, psychomotor retardation and normal stature.*

? Trisomy 21

Result: 46,XY

14. *Chinese boy aged 4 years, with speech delay and short stature.*

? Trisomy 21

Result: 47,XY + 21

15. *Female, aged 17 years, of mixed ethnic origins, with mild mental retardation, stunted stature and single simian crease.*

? Trisomy 21

Result: 47,XX + 21

CHAPTER 14

MENTAL RETARDATION ON MAURITIUS: DISCUSSION

14.1 INTRODUCTION

In this chapter, the classification used in this survey is briefly discussed and the findings are compared with those of similar studies. Finally, the results obtained in each aetiological category are analysed and reviewed. The provisionally private syndrome (PPS # 1-9) are described in Chapter 15.

14.2 AN AETIOLOGICAL CLASSIFICATION OF MENTAL RETARDATION

Five aetiological categories of retardation were chosen and used in the Mauritian survey. They proved useful in this clinical setting, were practical for management and counselling purposes and have the potential to accommodate the inevitable changes that will arise as new techniques and expertise are introduced onto the Island.

14.3 A COMPARATIVE STUDY OF THE MAIN CATEGORIES OF SEVERE MENTAL RETARDATION (SMR)

Opitz et al, (1978) and Fryns et al, (1986) undertook genetic and diagnostic institutional surveys in the USA and Belgium that were similar to the present study and thus afford comparison. In Table 14-I a summary of the percentage totals for each category of SMR in these two surveys is contrasted with those of the Mauritian study.

	Present Survey	Fryns et al	Opitz et al
Syndromic MR	36,2	38,7	21,3
(Contribution by Trisomy 21)	(27,6)	(12,7)	(7,3)
CNS Malformations	2,0	4,6	16,2
CP and/or epilepsy	23,5	34,1	33,7
Acquired	11,2	9,2	13,0
Undiagnosable MR	27	13,3	16,2
	99,9	99,9	100,4

Table 14-I: A comparative study of three aetiological surveys of SMR.

Comparisons between surveys have many inherent problems and cognisance must be taken of the influences that can bias a sample of mentally handicapped individuals. For certain institutions, the nature of the in-patient population may be determined by factors such as the facilities available, the

specialised rehabilitation programmes which are offered and the public reputation. On a remote island such as Mauritius, however, the population of MR individuals is unlikely to be biased by these influences as the emigration or immigration of severely retarded individuals is very infrequent.

14.3.1 Syndromic MR

In the Mauritian survey, trisomy 21 is the major contributor to the category of syndromic mental retardation - (27,6%) compared to the figures published by Fryns (12,7%) and Opitz (7,2%). Two reasons might account for this discrepancy: firstly, in the present survey, there was a high referral rate for trisomy 21 as it is an easily recognisable disorder; secondly, antenatal screening and termination of pregnancy is not undertaken on Mauritius whereas the practice is common in both countries under comparison.

14.3.2 Undiagnosable MR

Undiagnosable mental retardation represented 27% of the severely handicapped individuals, a figure almost double that of the other studies. A lowering of the percentage contribution of this group can be expected in the future with the advent of new investigatory facilities on the Island. The high incidence of CNS malformations found in the study reported by Opitz et al, probably reflects the investigator's utilisation of sophisticated radiographic scanning facilities.

14.3.4 Acquired MR

The environmental causes for MR in the Mauritian sample are numerically similar to those of the other studies. However, this subcategory may be under-represented since the prime aim of the survey was the investigation of genetic rather than acquired disease.

14.4 THE "TWO GROUP APPROACH" TO MENTAL RETARDATION

For a genetic survey, a subdivision of mentally handicapped individuals into two groups based upon the level of IQ, is valid on the basis of theoretical and empirical observations (Penrose, 1966; Moser and Wolf, 1971). It also proves to be of practical value when assessing institutions.

The rationale behind this "two group" approach has already been alluded to in paragraph 12.2.3 and is further elucidated in Fig. 14-1. This diagram illustrates how human intelligence in terms of accepted testing procedures, lies within a normal Gaussian distribution. Certain individuals will therefore fall below the range of two standard deviations (IQ < 70) in the absence of organic pathology. This group has been labelled variously as "physiological", "cultural-familial" or "polygenic" and is represented graphically by the blue hatching in the diagram. Other individuals exist who are mentally handicapped due to organic disease. These are the "pathological" or "nonpolygenic" group (red hatching). (Penrose, 1966; Telfer and Cowell, 1981.) Although the majority of individuals falling into the range of severe mental retardation (IQ < 50) have organic brain pathology, overlap between the two groups clearly exists.

A comparison between severe and mild MR has been presented in this study. In reviewing Table 13-I, the prevalence of known syndromes in individuals with MMR (12,6%) is less than those cases with SMR (36,2%). Conversely, in the category of

undiagnosable MR, the total for MMR is 68,5% compared to 36,2% for SMR. Furthermore, in the MMR group, the majority of mildly retarded individuals (83%) had no additional dysmorphism and 30% were familial. These findings present strong evidence for the contribution of "physiological/ polygenic/cultural-familial" factors in the aetiology of persons with mild mental retardation. The relative contribution of genetic disease to mild mental handicap on Mauritius is in keeping with the results of other studies (Moser and Wolf, 1971).

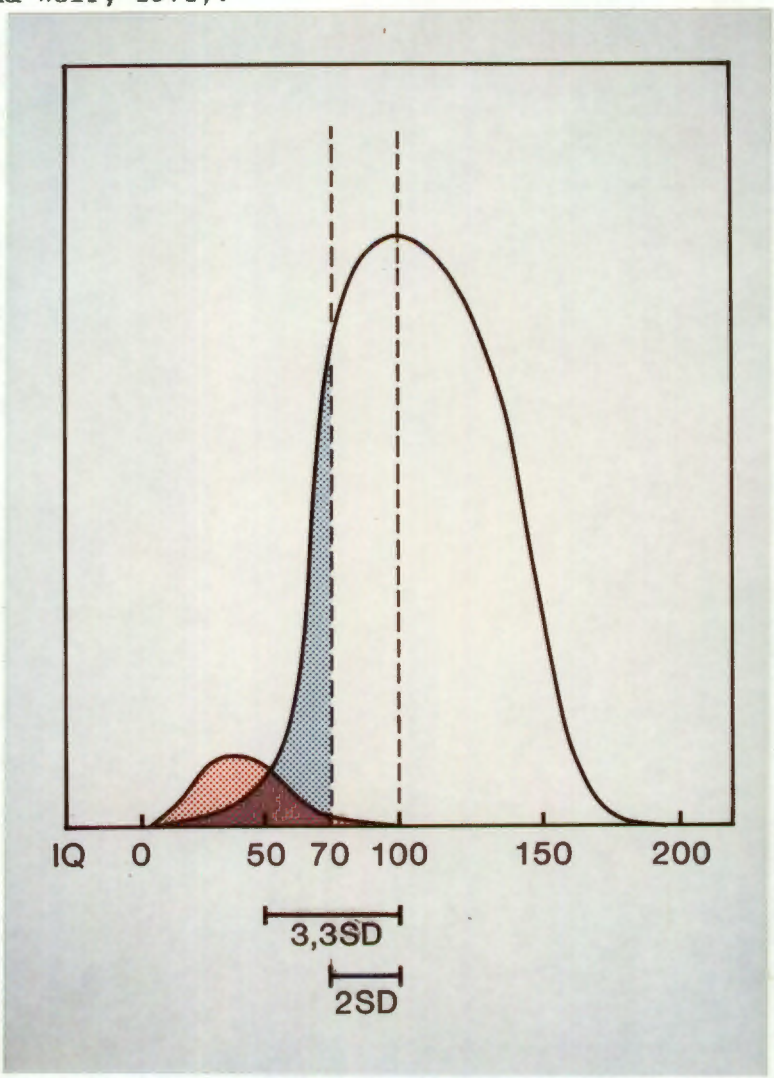

Fig. 14-1: The 'double-bell' distribution of intelligence: Blue hatching represents the "physiological' group of mental retardation; red hatching incorporates the "pathological" group.

14.5 SYNDROMIC MENTAL RETARDATION

14.5.1 Chromosomal Abnormalities: Introduction

Chromosomal aberrations associated with mental retardation are found in approximately 20% of individuals in institutions (Nelson and Smart 1982, Rasmussen et al, 1982; Fryns et al, 1984). Trisomy 21 is a common disorder in all studies.

High resolution banding and more recently, prometaphase banding, have enabled cytogeneticists to identify deletions and translocations which were previously undetectable. The recognition that an interstitial deletion of the long arm of chromosome 15 is found in about 50% of the patients with Prader-Willi syndrome, (Ledbetter et al, 1981) could herald the finding of similar abnormalities in, for example, the Cornelia de Lange or Rubinstein-Taybi syndromes (Baraitser, 1986).

The fragile X or Martin-Bell syndrome, first described by Lubs (1969), has emerged as a common cause of mental retardation in males. The male phenotype is varied and subtle and non-penetrance may occur (Fryns 1984). Variable degrees of mental retardation are present in approximately one third of female carriers with this disorder (Bundey et al, 1985). Cytogenetic screening is the most efficient means of detecting affected individuals (Turner et al, 1986).

14.5.2 Chromosomal Abnormalites on Mauritius

At present, there are no facilities for karyotyping on the Island of Mauritius. During the survey, a limited number of people were selected for cytogenetic analysis. (See paragraph 13.8.) Most persons with Trisomy 21 were diagnosed on clinical grounds but chromosomal confirmation was sought in certain instances, where the phenotypic features were equivocal or atypical (Fig. 14-2).

Fig. 14-2: A Chinese girl with learning difficulties and clinodactyly in whom a trisomy 21 karyotype was confirmed.

The Prader-Willi syndrome was diagnosed phenotypically in 3 individuals and, in one instance, a 15p deletion was detected on chromosomal examination (Fig. 14-3). A child with the Prader-Willi phenotype and oculo-cutaneous albinism is further discussed in paragraph 14.6.2.

Fig. 14-3: The Prader-Willi syndrome in a young boy with a 15p- karyotype.

A male infant with severe mental retardation had a 15p+ karyotype. This may be an incidental finding but no other cause for his handicap could be demonstrated.

No examples of the fragile X syndrome were found. Three families with affected brothers who had at least three of the typical clinical findings for the Martin-Bell syndrome were analysed for Xq27 deletions but no fragile sites could be detected.

14.5.3 Malformation Syndromes with Mental Retardation

The aetiological delineation of certain malformation syndromes is still unclear and for the purposes of this study, they are classified separately. The Rubinstein-Taybi syndrome was diagnosed in one severely retarded individual (Figure 14.4). Evidence for a genetic aetiology in this condition is mounting (Gillies and Roussounis, 1985; Berry, 1987) and heterogeneity has been proposed. The most unifying aetiological hypothesis is that the disorder represents a chromosomal microdeletion. A single case of the epidermal naevus syndrome with hemihypertrophy and mental retardation is described in greater detail in Chapter 19.

Fig. 14-4: The Rubinstein-Taybi syndrome.

14.6 MENDELIAN FORMS OF MENTAL RETARDATION

The 14 individuals with syndromic mental retardation attributed to a "single gene defect" are tabulated in paragraph 13.4.2. Those with unique or unusual features warranting further mention are discussed below. Brief case reports are provided.

14.6.1 Tuberous Sclerosis

Two sporadic unrelated Hindu boys with mental retardation had the classical features of tuberous sclerosis. In one, (Figure 14-5) single digit macrodactyly simplex congenita was present.

Fig. 14-5: Tuberous sclerosis: Mental retardation, adenoma sebaceum, ash leaf spots and single digit macrodactyly are present.

Overgrowth of a limb or digit is previously unreported in tuberous sclerosis although well recognized in the other phakomatoses such as neurofibromatosis and the Sturge-Weber syndrome (Tentamy and Rogers, 1976). The presence of this abnormality in a Mauritian boy may be further evidence of an underlying unifying pathogenetic mechanism for the phenotypic similarities of these neurocutaneous syndromes.

Fig. 14-6: A mentally retarded boy with tuberous sclerosis: areas of depigmentation and a large shagreen patch are cutaneous manifestations of this gene.

14.6.2 Prader-Willi syndrome with albinism

A Chinese girl with albinism presented at birth as a floppy baby. The first six months of her life were characterised by feeding difficulties, hypotonia and global developmental delay. As a toddler she displayed a voracious appetite which has persisted. At the time of examination, aged 6 years, she was noted to be obese with small hands and feet, mental retardation and oculo-cutaneous albinism (Fig. 14-7). Her parents were unrelated and there was no contributory family history. Chromosome analysis, including high resolution banding, yielded normal results.

Fig. 14-7: Albinism and a Prader-Willi phenotype in a Chinese girl aged 6 years.

This girl has features of both the Prader-Willi syndrome and albinism. Recently, attention has been drawn to the association between this syndrome and hypopigmentation (Hittner et al, 1982; Creel et al, 1986). Wiesner et al (1987) concluded that albinism may be associated with a deletion of the long arm of chromosome 15 in almost 50% of cases and Phelan et al (1988) described ablinism in a black child with a deletion of 15q 11.2. The clinical features in this patient may be the consequence of a microdeletion, too small for detection by current cygtogenetic techniques, that results in the Prader-Willi phenotype and encompasses the gene for recessively inherited oculo-cutaneous albinism. The affected girl was presumably heterozygous for the albinism gene, but the phenotype resulted from loss of the corresponding normal allelle in the putative microdeletion.

14.7 METABOLIC DISEASE

Genetic metabolic disease represents a small component of the known causes of mental handicap (Opitz et al, 1978). These conditions were not specifically included in the Mauritian survey because of the technical and logistical difficulties in a laboratory diagnosis.

There are few clinical and dysmorphic clues to the diagnosis of the inborn errors of metabolism and the pickup rate for metabolic screening of undifferentiated mental retardation is less than 5% (Thoene et al, 1981). (Examples of notable exceptions include the mucopolysaccharidoses and homocystinuria.) However, certain metabolic disorders had already been identified on previous occasions in Mauritian patients and these are briefly reviewed below.

14.7.1 Phenylketonuria

A girl aged 3 years, with fair complexion and mental retardation was investigated in early childhood at an overseas centre and found to have markedly elevated phenylalanine levels. Both parents were of French descent but the families had been resident on Mauritius for five generations. They claimed to be "the only two unrelated Franco-Mauritians". However, there is a strong likelihood that they are in fact consanguineous.

The presence of the gene for phenylketonuria amongst this population group is of considerable importance. The disease

prevalence is insufficient to warrant the institution of a national screening programme but a high index of suspicion for this treatable condition in the Franco-Mauritian populace, would be perspicacious practice.

14.7.2 Tay-Sachs disease

Tay-Sachs disease was suspected in a purportedly non-consanguineous Franco-Mauritian family in which two children had died in early childhood following a neurodegenerative illness. An adolescent sister of the deceased infant, was subsequently proven to be a heterozygote carrier for Tay-Sachs disease in the laboratories of the Department of Human Genetics, Cape Town. This autosomal recessive disorder has similar genetic implications for the Franco-Mauritian community as those of phenylketonuria.

In addition to the well documented presence of Tay-Sachs disease in persons of Ashkenazi Jewish stock, a high prevalence of this disorder has also been found in the non-Jewish, French-Canadian population of Quebec (Andermann et al, 1977). It is interesting to speculate that the faulty gene in the Franco-Mauritian community may be of similar origin. Two genetic mechanisms, working together, might account for this situation: Heterozygous carriers of French origin may have introduced the Tay-Sachs gene, by a founder effect, to both the Mauritian and Quebec communities. As both populations are isolated and endogomous, in-breeding would subsequently result in a comparatively high incidence of the homozygous form for this disorder.

14.7.3 Lesch-Nyhan syndrome

A 6 year old Hindu male with profound mental retardation, cerebral palsy and self mutilation was found to have significantly raised serum uric acid levels. No other male relatives were affected and no other instances of this rare X-linked syndrome were encountered during the survey.

14.7.4 Cretinism

Both non-genetic forms and Mendelian inheritance of cretinism are known to occur. In the absence of tests for thyroid function, the exact aetiology of untreated congenital hypothyroidism with mental retardation on Mauritius was unknown. The disorder was therefore classified in the miscellaneous subcategory of syndromic mental retardation.

14.8 CNS MALFORMATIONS

Essential facilities for the diagnostic confirmation of CNS malformations are not available on the Island. For the present time, this category caters for diagnoses established in centres abroad and these disorders are almost certainly under-represented.

14.9 CEREBRAL PALSY AND/OR EPILEPSY

Persons with cerebral palsy and/or epilepsy, represented 19% of all mentally retardated individuals on the Island. Comprehensive ascertainment and further analysis of patients in this group was beyond the scope of this thesis.

14.10 ACQUIRED MENTAL RETARDATION

Environmental factors accounted for 10% of mentally handicapping disorders on Mauritius, a figure in keeping with the findings in similar surveys. Two causes were notably absent: the foetal alcohol syndrome was not detected and no instances of childhood battering were found. Both these entities are well-documented aetiologies in acquired MR and their absence possibly reflects the socio-religious views of the Mauritian community.

Cytomegalovirus (CMV) is a common microbiological cause of prenatally acquired mental handicap (Stern and Tucker, 1973). The incidence of CMV infection on Mauritius is unknown as serological testing is not available. If congenital CMV is present, the affected individuals are likely to have been classified in the category of undiagnosable mental retardation, as there are no pathognomonic clinical features.

14.11 UNDIAGNOSABLE MENTAL RETARDATION

This category is essentially heterogeneous and of considerable importance both academically and practically. The sub-categorisation into sporadic and familial groups, with or without dysmorphic features, is of clinical value. These subdivisions will allow for the reappraisal of cases when new knowledge concerning syndrome identification emerges. In addition, the progression and natural history of a disorder may provide additional diagnostic clues. Similarly, the birth of further affected family members may help establish an inheritance pattern.

The allocation of a separate category for children with autism is controversial. The numbers in this survey were small (7 individuals including 3 siblings). No additional clinical features were evident in these children, who were arbitrarily regarded as being severely retarded, in the absence of specialised intelligence testing. For these reasons, a separate categorisation seemed appropriate for the Mauritian study.

Nine individuals were considered to have provisionally private syndromes (PPS) and are grouped within the section on undiagnosed mental retardation with additional dysmorphism.

14.12 FINAL COMMENT

Institutional screening can provide important information to parents, teachers and health care personnel about the causes of mental handicap. However, the question of appropriate diagnostic testing deserves further attention. Batteries of invasive tests applied in a blanket approach, have rarely proved worthwhile. In the Mauritian setting, it is questionable whether highly spohisticated, costly, labour intensive evaluation of all mentally retarded individuals is justifiable. A detailed family history and careful physical examination would probably be adequate in most instances. One possible exception is that of karyotyping. Many workers in this field consider that all retarded children and adults should undergo chromosome analysis (Baraitser, 1986).

The contribution of genetic disease to mental handicap, both mild and severe, has been documented for the Island of Mauritius. Both well-known and rare entities were encountered, and certain conditions, such as the fragile X syndrome and foetal alcohol syndrome, are conspicuous by their absence.

CHAPTER 15

MENTAL RETARDATION: PROVISIONALLY PRIVATE SYNDROMES (PPS)

15.1 INTRODUCTION

This chapter contains a brief description of nine 'provisionally private' mental retardation syndromes. In the classification expounded in Chapter 13, these entities were allocated to the category of *undiagnosed mental retardation with additional dysmorphism*". Random 'PPS' numbers were given to these disorders and this numerical designation is preserved in the discussion which follows.

The affected individuals or families discussed in this chapter all had associated features which were suggestive of syndromic autonomy. However, personal communication with colleagues in specialised fields, advice sought and received from experts abroad and utilisation of the Birth Defects Information Service computer programme, failed to provide a satisfactory diagnosis. The term 'provisionally private' would thus seem appropriate until such time as independent syndromic status for these disorders is established or refuted.

15.2 NINE PROVISIONALLY PRIVATE SYNDROMES (PPS)

PPS # 1: Severe mental retardation in three brothers with Marfanoid habitus.

Three brothers, aged between 15 and 25 years, were referred with severe mental retardation. There was no relevant family history, the parents were unrelated and their fourth child, a daughter, was unaffected. The 3 boys bore a strong phenotypical resemblance to each other with large ears, long facies and high arched palates. They were all taller than 185 cm and two had an arm-span that exceeded their height by more than 5 cm. In two boys, the fingers were hypermobile and one had a single simian crease. All 3 brothers had normal secondary sex characteristics with average testicular size although body hair was minimal. The karyotype was 46,XY in each instance and no fragile sites were detected.

The brothers bear a similarity to two sets of mentally retarded brothers reported by Fryns and Buttiens (1987). These authors documented the dysmorphic features of a marfanoid habitus with cranio-facial abnormalities including a long face, a high arched palate and small mandible. Lujan et al (1984) had previously described a similar case and Fryns and Buttiens proposed this phenotype as a separate XL mental retardation syndrome, distinguishing it from over 70 other previously reported XL syndromes in which mental retardation was a major component. (McKusick, 1986). It is possible that the 3 mentally retarded Marfanoid Mauritian brothers had this entity (Fig. 15-1).

Fig. 15-1: Mentally retarded brothers with a Marfanoid habitus and dysmorphic facial features.

PPS # 2: Multiple congenital abnormalities in an offspring of consanguineous parents.

A Muslim boy, aged seven years, was the only child of consanguineous parents. He had a birth weight, at term, of 1,5 kg and during infancy was found to be profoundly and globally retarded with spasticity, microcephaly, blindness and convulsions. His face and chest were asymmetrical. There was no history of maternal rubella, perinatal anoxia or trauma. Chromosome analysis was normal.

This individual presents problems in classification and counselling. No syndromic diagnosis could be made; the multiple handicap was suggestive of a chromosomal abnormality, yet none was found. The features are also compatible with a prenatally acquired infective aetiology but equally the parental consanguinity could be indicative of autosomal recessive disease. The parents were given a guarded prognosis concerning recurrence risks for further offspring.

PPS # 3 **Multiple congenital abnormalities in a brother and sister.**

A boy, aged 6 years, and his sister aged 1 year, were the only offspring of a closely consanguineous couple. The clinical stigmata and psychomotor development of their children were identical and included the following features: an inability to perform any motor or intellectual task, convulsions resistant to therapeutic control and spasticity - worse in the boy than the girl and considered to reflect the benefits of better seizure control in the latter. Cranio-facial dysmorphology included dolicocephaly, cleft palate, bulbous nose, microcornea and aphakia. Both children had sparse hair and eczema that increased in severity with time. The girl had undergone a CT scan that demonstrated "agenesis of the corpus callosum with ventricular dilatation and thickening of the optic nerves". Chromosome analysis in both children was normal.

These siblings have previously been mentioned in the section on blindness. An autosomal recessive syndrome seems likely but in spite of the clear-cut phenotypic features no diagnosis could be reached.

PPS # 4: **Progressive psychomotor dysfunction in siblings.**

Two sisters, the only offspring of consanguineous Hindu parents, presented with the history of a deterioration in psychomotor function after 6 months of age. Development before 4 months, carefully documented in their second child, was entirely normal. When examined at the ages of 3 years and 6 years respectively they were found to have minimal power in limbs and trunk, marked hypotonia, muscular wasting, inability to follow light and absent speech. Hearing appeared intact. There were no joint contractures or dysmorphic features. Screening for metabolic disease at a centre in France had been unrewarding; ultrasonic scanning demonstrated cerebral atrophy and chromosomal studies repeated in Cape Town were normal.

The "best fit" diagnosis in the absence of further investigations was some form of spinal muscular atrophy and mental retardation with autosomal recessive inheritance.

PPS # 5: Mild mental retardation with limited elbow extension.

A Muslim girl, aged 10 years and her younger brother had mild mental retardation and a thirty degree limitation of full elbow extention. Flexion and rotation were normal, there were no other skeletal problems and no additional dysmorphology. The parents were first cousins.

This syndrome of mental retardation and limitation to full elbow extention was observed in another unrelated individual with severe mental retardation (documented in Table 13-V) and also in PPS # 7. The sibling pair described here did not fit any previously described entity and must therefore remain "provisionally private".

PPS # 6: Multiple congenital abnormalities including polydactyly, cleft lip and palate and global developmental delay. (Fig. 15-2)

A male, aged four years, of Hindu extraction was the only affected child of 3 offspring from a non-consanguineous union. Following a normal pregnancy and delivery, the following congenital abnormalities were noted: bilateral cleft lip and palate, low posteriorly rotated ears with simple helix formation, an antimongoloid slant to the eyes, bilateral clinodactyly and post-axial polydactyly of the right hand. Psychomotor development was globally delayed. He began to walk at age 3, but by 4 years could only comprehend simple instructions and was unable to speak. Epileptic seizures commenced in early infancy. Vision and hearing were normal. Chromosomal analysis revealed a 46,XY karyotype.

No diagnosis could be made for this child. Although many of the phenotypic features might be ascribed to the action of an environmental agent during early embryonic life, polydactyly would be unusual in these circumstances.

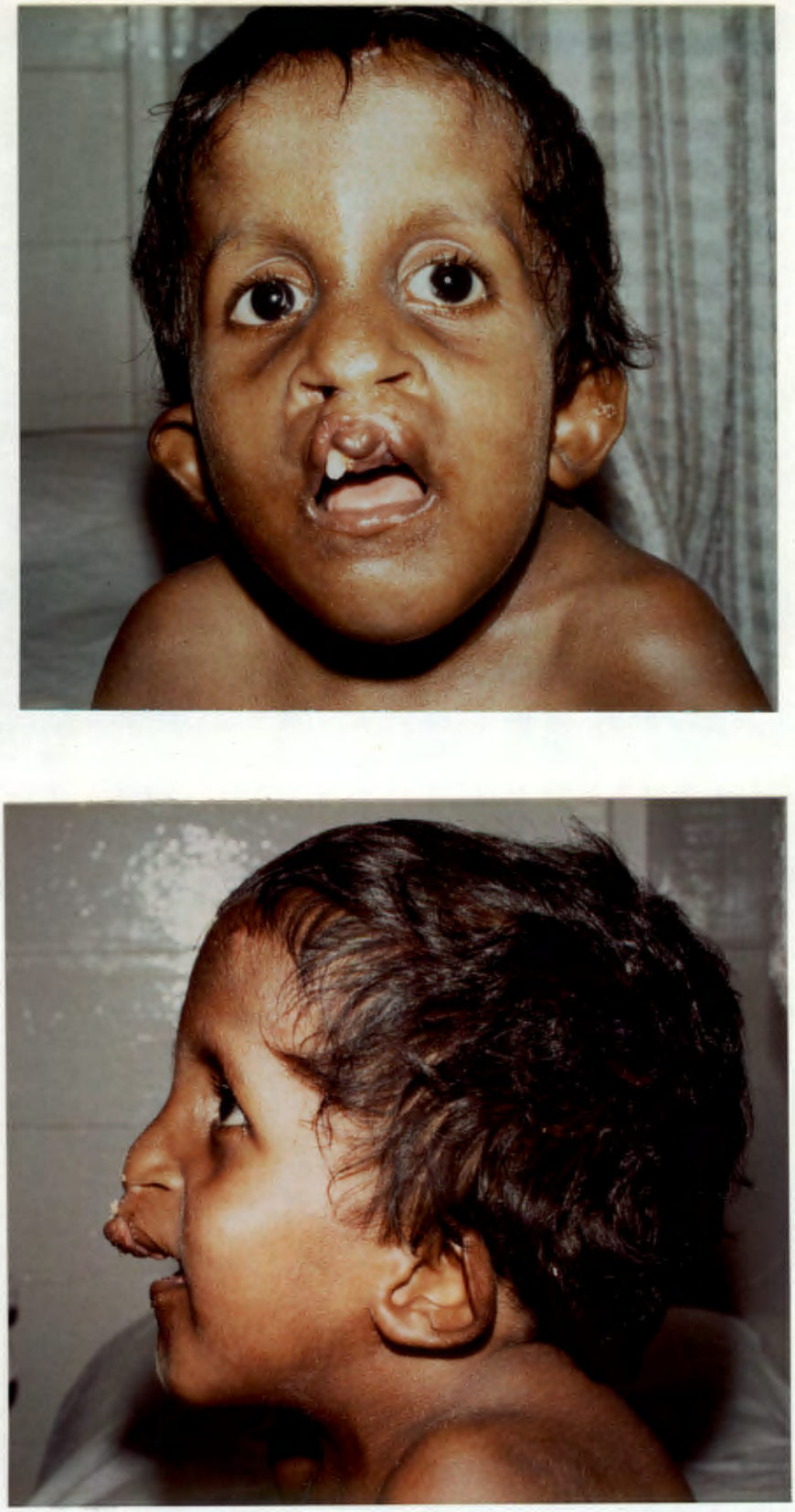

Fig. 15-2: A boy aged 4 years, with global psychomotor retardation, a cleft lip and palate, low slung simple ears and antimongoloid slant to the eyes (PPS # 6).

PPS # 7: Mild Mental retardation, Marfanoid habitus and limited elbow extention.

A boy, aged 10 years, was the fourth of seven sons, three of whom demised in infancy from unknown cause. No other family members were affected. He had the following dysmorphic features: a marfanoid habitus, arachnodactyly, a triangular shaped face and high arched palate (Fig. 15-3). His height was 157 cm (>97 centile) and his head circumference was 58 cm (>97 centile); his IQ fell within the 50-70 range. A wide carrying angle was exaggerated by limitation to full elbow extention beyond 150 degrees. All other joints were clinically normal in structure and range of movement. Radiographic studies demonstrated fusion of the fronto-parietal sutures with normal bony anatomy of the elbow joint. Chromosome analysis yielded a 46,XY karyotype.

The combination of mental retardation and marfanoid habitus has been alluded to in PPS # 1. This boy fits many of the features described by Fryns and Buttiens (1987). However, elbow abnormalities have not been previously documented and may represent a new dimension to the phenotype. Incomplete elbow extention and mental retardation was also a feature of PPS # 5.

Fig. 15-3: Boy, aged 10 years with mild mental retardation, Marfanoid habitus, a wide carrying angle and large head circumference.

PPS # 8: Severe mental retardation, dwarfism and coarse facies.

An institutionalised adult male with severe mental retardation was found to have the following features: height 126 cm, head circumference 50 cm, with proportionate limb length, fully developed secondary sex characteristics and normal testicular size. His face was markedly dysmorphic with large cupped ears, a broad coarse nose, micrognathia, heavily lidded eyes and prominent supra-orbital ridges. In addition, there were bilaterally abnormal creases, brachydactyly, clinodactyly and broadening of the thumbs (Fig. 15-4 and Fig. 15-5). No past history was available and permission for further investigations could not be obtained.

A firm diagnosis has not been forthcoming despite the many distinctive clinical features. This case illustrates and re-emphasizes the difficulties in the syndromic diagnosis of adult patients where growth and ageing may distort the familiar stigmata of recognizable childhood syndromes.

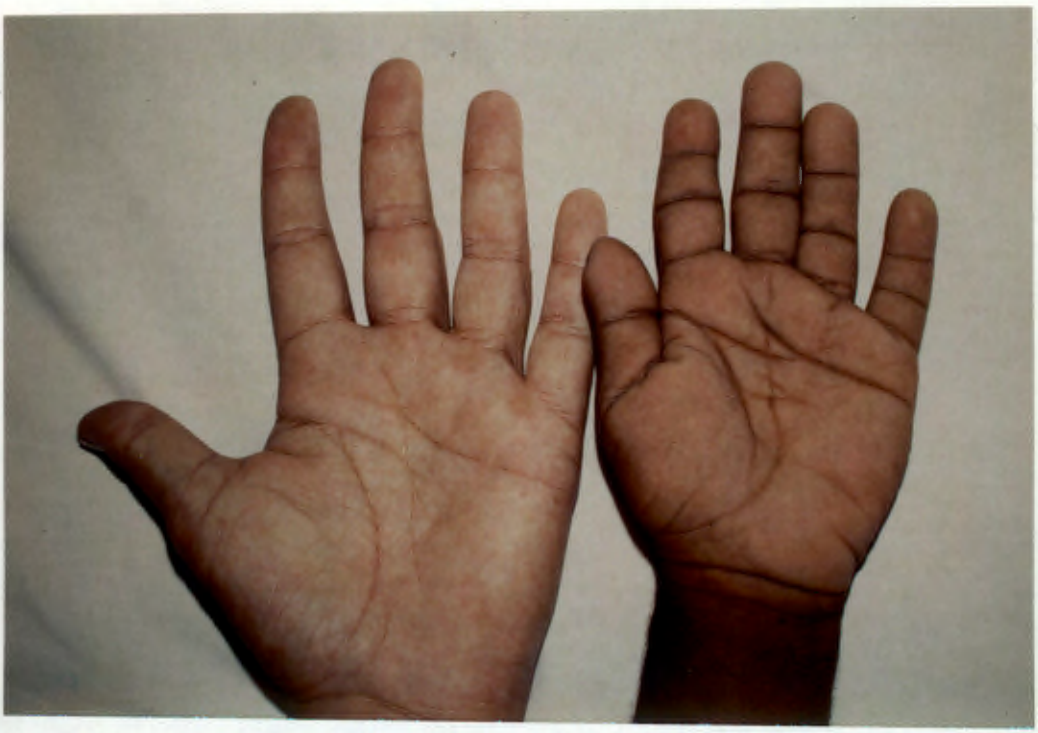

Fig. 15-4: PPS # 8: The hand (right) has brachydactyly, clinodactyly, abnormal creases and broad thumbs.

Fig. 15-5:

PPS # 8: A mental retardation syndrome with dwarfism and distinctive facial features, alone and together with the investigator, beneath a tree in the late afternoon sun.

PPS # 9 **Mild mental retardation with abnormalities of the nasal tip, ears, fifth fingers and palmar creases.**

An Indian male, aged 14 years, with a non-contributory family history presented with mild mental retardation, absence of the tip of his nose, shortening of both fifth fingers maximal in the terminal phalanges, bilateral simian creases, posteriorly placed thumbs and crumpled ear lobes (Fig. 15-6).

No previous reports of a similar case could be found and no diagnosis could be reached.

Fig. 15-6: A teenage boy with an absent tip of nose, simian crease, posteriorly placed thumbs and short fifth fingers.

15.3 FINAL COMMENT

Problems arose, during the assessment of individuals for inclusion in this chapter, with the interpretation of clinical features which could be normal variants. Many of the stigmata forming a part of these provisionally private syndromes are often present in the normal population; indeed, care was taken to avoid over-emphasis of such signs during the institutional screening.

It is likely that certain patients depicted in this chapter have genetic syndromes which have not been documented previously. It can be anticipated that the accummulation of reports of this type will ultimately facilitate complete delineation and the establishment of syndromic identity.

SECTION VI

PHYSICALLY DISABLING GENETIC CONDITIONS ON MAURITIUS

Genetic disorders of stature or locomotion which result in a physical disability and dermatological diseases that lead to disfigurement, are presented and discussed in this section.

Chapter 16: A survey of physically disabling conditions on Mauritius: aims, methods and results.

Chapter 17: Genetic disorders of the skeleton: findings and discussion.

Chapter 18: Genetic neuromuscular disorders: findings and discussion.

Chapter 19: Genetic disorders of the skin and exocrine glands: findings and discussion.

CHAPTER 16

A SURVEY OF PHYSICALLY DISABLING CONDITIONS ON MAURITIUS: AIMS, METHODS AND RESULTS

16.1 INTRODUCTION

An assessment of the contribution of those genetic disorders where physical disability is a predominant handicap, has been undertaken on the Island of Mauritius.

The descriptive term 'physical disability', used in its broadest sense, includes any disturbance of locomotion or stature that results in some degree of functional impairment. The extent of the handicap may vary from trivial to incapacitating and is dependent, in part, on the individual's needs and expectations.

Many conditions that result in blindness, deafness or mental retardation may, in addition, present with varying degrees of physical disability - indeed, numerous examples can be found in the relevant chapters of this thesis. In these cases, however, for management and educational purposes, the physical impairment is of secondary priority. The disabled individuals who form the subject of this section have, with few exceptions, a physical handicap that is of central importance to their rehabilitation and care.

In addition, to skeletal and neuromuscular conditions, certain inherited disorders of the skin which cause significant incapacity by virtue of their deleterious effect on cosmetic appearance have been included in this section.

The aims, methods and an overview of the results of a survey into physically disabling conditions on Mauritius are discussed in this chapter. During the ascertainment of affected individuals, acquired forms of physical handicap were encountered. As these conditions may superficially resemble genetic entities and are important in the assessment of the relative contribution of genetic disease to physical disability, a brief description of the acquired aetiologies is presented at the end of this chapter.

16.2 AIMS AND METHODS

The aim of the survey was to assess the contribution of genetic disease towards physical and cosmetic disability on Mauritius. Individuals included in the study were selected if their functional limitation was permanent and not severely compromised by additional handicapping disorders. For ease of categorisation and presentation, the inherited physically handicapping disorders were divided into the following sub-groups and given self-explanatory descriptive titles:

i) Genetic disorders of the skeleton; (Chapter 17)

ii) Genetic neuromuscular disorders; (Chapter 18)

iii) Genetic disorders of the skin and exocrine glands; (Chapter 19)

16.2.1 Sources of Referral and Ascertainment

Institutionalisation of physically disabled individuals may not be necessary as rehabilitation programmes generally attempt to integrate such persons into normal social and vocational circles. Occasionally, sheltered employment is required and hospital care may be essential during the terminal stages of some conditions such as Duchenne muscular dystrophy. In an attempt to achieve a representative ascertainment of afflicted individuals the following sources were utilised:

i) The Physically Handicapped Workshop Association (PHWA)

The PHWA caters for the needs and welfare of physically handicapped people and their families on Mauritius. The association has approximately 250 members and arranges workshop training, job placement and social integration. The records of the members were studied and those individuals in whom a genetic diagnosis was suspected on clinical or genealogical grounds were contacted and assessed at the premises of the PHWA. Using this approach, 42 physically disabled persons were documented.

ii) Fraternité Mauricien des Malades et des Handicapès (FMMH)

The FMMH provides workshop and training facilities for the physically handicapped at a number of centres on Mauritius. These institutions were visited on pre-arranged days and all the members present were examined. Seventy-five individuals fitted the criteria enunciated in paragraph 16,2 and were included in the survey.

iii) United Skills

This organisation caters specifically for the employment of the disabled. There was no age limit and the only criterion for appointment to a vacant position was the ability to contribute in some way to productivity. Regular staff totalled 20 individuals; 12 had a predominant physical disability and were included in the survey.

iv) Occupational Therapy

The indefatigable efforts of Mme Jacqueline Laurent, the peripatetic occupational therapist for the Island, were instrumental in the documentation of all known cases of muscular dystrophy on Mauritius. These 19 individuals were assessed at their homes with the help of the staff of the Association de Parents d'Enfants Inadaptés l'Ile Maurice (APEIM).

v) Local Medical Practitioners and Specialists

The referral, by local practitioners, of patients with suspected genetic disorders was a valuable source of information; many of the dermatological conditions were documented in this way. Dr P. Taikie, Orthopaedic Surgeon at Victoria Hospital, Candos, gave invaluable assistance by facilitating contact with patients with skeletal anomalies and presenting them for assessment.

vi) Vivre Debout (Fig. 16-1)

This home, established in 1981, is modelled on a similar organisation in France. Physically handicapped adults live independently, supporting themselves financially by home industries such as book-binding and greeting-card manufacture. Six individuals were assessed.

Fig. 16-1: Vivre Debout: Members of the household.

16.2.2 Method of Investigation

In each instance relevant historical data was obtained from the patient or family and, if appropriate, a pedigree was constructed. This information, together with a clinical examination readily facilitated assignment to one of the main categories of handicap (paragraph 16.2). Radiographic studies were undertaken in selected individuals. No facilities were available for electromyography or histological examination of skin, hair or muscle.

Where a diagnosis was not initially reached, the assistance and advice of overseas experts in specific specialised fields was sought after analysis of the survey data.

16.2.3. Additional Comment

For the purposes of this study, the categories of physical disability used were accommodating and appropriate. As with most classifications, flexibility was required and 'best fit' allocations negated the need for miscellaneous categories.

No attempt was made at full ascertainment of multifactorial conditions such as spina bifida and talipes equino-varus. The nature of their aetiology demands an independent study, with an emphasis and enquiry that is beyond the scope of this thesis. Nevertheless, as these entities were encountered during the Mauritian survey, their presence has been documented (for convenience under the category of skeletal disorders), without further study or discussion.

16.3 RESULTS

During the survey, 174 physically handicapped individuals were investigated. A division into aetiological and pathological groups is provided in Table 16-I. The 3 categories of genetic disorders contribute 46% of the total for physically disabling conditions and are discussed in detail in the succeeding chapters of this section.

Acquired factors accounted for the disability in 94 (54%) of affected individuals. These persons were encountered incidentally during institutional screening and were not actively or comprehensively documented. Nonetheless, acquired aetiologies represent a significant contribution to the total for physical handicapping disorders on Mauritius

and a brief analysis and discussion is presented in the remainder of this chapter.

AETIOLOGY	PATHOLOGICAL GROUP	TOTAL	PERCENTAGE
Genetic	Skeletal	45	
	Neuromuscular	28	
	Skin, including the ectodermal dysplasias	7	
	Total	80	46%
Acquired		94	54%
TOTAL		**174**	**100%**

Table 16-I: A categorisation of 174 physically disabled individuals into aetiological and pathological groups.

16.4 ACQUIRED CAUSES OF PHYSICAL DISABILITY

During the screening of the FMMH and following the assessment of referred cases, 94 individuals with an isolated physical handicap ascribed to acquired aetiologies were encountered. A broad analysis of the causes is presented in Table 16-II.

CAUSE	TOTAL	PERCENTAGE
INFLAMMATORY DISORDERS	51	54,5%
Poliomyelitis	47	
Juvenile rheumatoid arthritis	1	
Osteomyelitis	1	
Perthes Disease	1	
Guillain-Barrè Syndrome	1	
CNS DISORDERS	37	39%
Cerebral palsy with normal mentation	33	
Cerebral vascular accident	4	
TRAUMA (including spinal injury)	2	2%
SURGICAL AMPUTATION	4	4,5%
Tumour	1	
Vascular pathology	3	
TOTAL	94	100%

Table 16-II: The acquired causes of physical disability in 94 individuals.

As reflected in table 16-II, the prevalence of handicap due to the sequelae of poliomyelitis is striking. In the mid 1950's, large epidemics of this infectious disease resulted in significant physical morbidity in Mauritius; many of the individuals documented during the survey were in the age group of 30-40 years and reflect this period in history. The establishment of oral polio vaccination (OPV) programmes on the Island over the last two decades has been highly successful. Ninety-six percent of all infants in 1985 received OPV in 3 doses (Brissonnette, 1986) and no cases of polio have been notified on Mauritius in the last two years. The geographical isolation of an island with its inbuilt quarantine facilities for the population, makes the total eradication of physically handicapping infectious diseases, like poliomyelitis, an attainable goal.

Individuals with cerebral palsy and normal mentation represented 33% of the total for acquired physical disability. For the remainder, a range of aetiological factors was found although it is clear that certain conditions such as cerebrovascular accidents were incompletely ascertained. It is generally accepted that road traffic accidents and war injuries are significant causes of physical handicap in many countries. On Mauritius, the contribution of the former was minimal and the latter was notably absent.

In the absence of new and unforeseen acquired aetiologies with improved perinatal care and the eradication of poliomyelitis, the proportionate contribution of genetic disease to physical handicap can be expected to increase substantially.

CHAPTER 17

GENETIC DISORDERS OF THE SKELETON: FINDINGS AND DISCUSSION

17.1 INTRODUCTION

The inherited skeletal dysplasias found on Mauritius are listed in Table 17-I, where they are classified according to their modes of inheritance. Certain conditions which were of special importance by virtue of their rarity, genetic significance or unusual concomitant features, have been prefixed with an asterisk. These entities are discussed in the remainder of this chapter with, if appropriate, brief case reports and illustrative photographs. Genetic diseases with classical phenotypes are not discussed further. The multifactorial disorders, as stated in paragraph 16.2.2, are mentioned only for completion.

INHERITANCE	DISORDER	TOTAL	NO. OF FAMILIES
AD	*Osteogenesis imperfecta (type I)	6	4
	*EEC syndrome with normal lip and palate	5	1
	Achondroplasia	3	3
	Syndactyly	3	1
	Camptodactyly	3	1
	Ehlers-Danlos syndrome (type III)	2	1
	Articular hypermobility syndrome	1	-
	*Fibrous dysplasia ossificans progressiva	1	-
	Hypochondroplasia	1	-
	*Pfeiffer syndrome	1	-
AR	Pituitary dwarfism	2	1
	*Pyknodysostosis	2	1
	*Spondylocostal dysostosis	1	-
Unknown	*Osteogenesis imperfecta	2	2
	Amniotic band syndrome	2	2
	Klippel-Feil Anomaly	2	2
	*Brachydactyly dwarfism and hip joint dysplasia	1	-
	*Enchondromatosis with dwarfism and deafness	1	-
Multi-factorial	Talipes equinovarus	2	2
	Spina bifida	3	3
Chromosomal	Turner syndrome	1	-

Table 17-I: Inherited disorders of the skeleton documented on Mauritius. [* = discussed further]

17.2 OSTEOGENESIS IMPERFECTA (OI)

OI is currently classified into four types based on the clinical and radiological changes and both AD and AR modes of inheritance have been recognised. Considerable heterogeneity is present at a clinical, biochemical and molecular level (Wallis et al, 1986) and difficulties arise in the accurate categorisation of some individuals, even with the assistance of sophisticated technology and specialist expertise. In Mauritius, OI was identified in 6 probands and 2 additional affected relatives were documented.

17.2.1 OI Type I

OI Type I (Osseous fragility, blue sclerae, AD inheritance) was diagnosed in a sporadic Franco-Mauritian boy, 2 Indian girls and a Hindu family with 3 affected members. The classical phenotype which was present in all these individuals, and the AD mode of inheritance in the Hindu family was further corroborative evidence which permitted a confident allocation to the subcategory OI type I.

17.2.2 OI - (Additional Types)

Two persons with OI illustrated some of the difficulties in accurate subclassification. These individuals are briefly described below:-

Case 1:

A female, aged 18 years, of Creole stock, had severe osseous fragility and had experienced many fractures with consequent crippling deformities. She had a severe kyphoscoliosis (Fig. 17-1) with stunted stature, white sclerae and dentinogenesis imperfecta. Her parents were not consanguineous and there were no affected relatives.

Fig. 17-1: A female, aged 18 years, with OI is severely deformed by a marked kyphoscoliosis and numerous fractures.

The phenotype of this young woman is compatable with OI type III (AR) or possibly type IV (AD) and clinical differentiation in this instance is impossible. The presence or absence of dentinogenesis imperfecta is of dubious value in subcategorisation (Gage et al, 1986).

OI type III is extremely rare (Sillence et al, 1986) and the vast majority of reported cases have been identified in the Black tribes of central and Southern Africa (Viljoen and Beighton, 1987). Although it might be argued that the rarity of OI type III reduces its likelihood as a diagnostic possibility in this Mauritian girl, nevertheless, as a member of the Creole community she does have close ancestral links with Africa. Studies at a biomolecular level will ultimately resolve this issue.

Case 2:

> *A newborn male of Creole stock, was born with several limb fractures and deformities of the skull and rib cage. Death from unspecified causes occurred at three weeks of neonatal life. Radiographic studies demonstrated thin ribs and well-modelled femora which presented an "apple-core" configuration (Fig. 17-2).*

Lethal perinatal OI is generally classified as "type II" and may represent either an AR form or a new AD mutation. However, the radiographic findings of case two, described above and depicted in Fig. 17-2, resemble type III (E Thompson, personal communication). Neonatal death is not incompatable with this sub-categorisation.

With advancing knowledge, many genetic entities are proving to be heterogeneous. These Mauritian individuals with OI serve to illustrate the difficulties of an accurate clinical allocation in a setting where the new molecular and biochemical technology is not yet available.

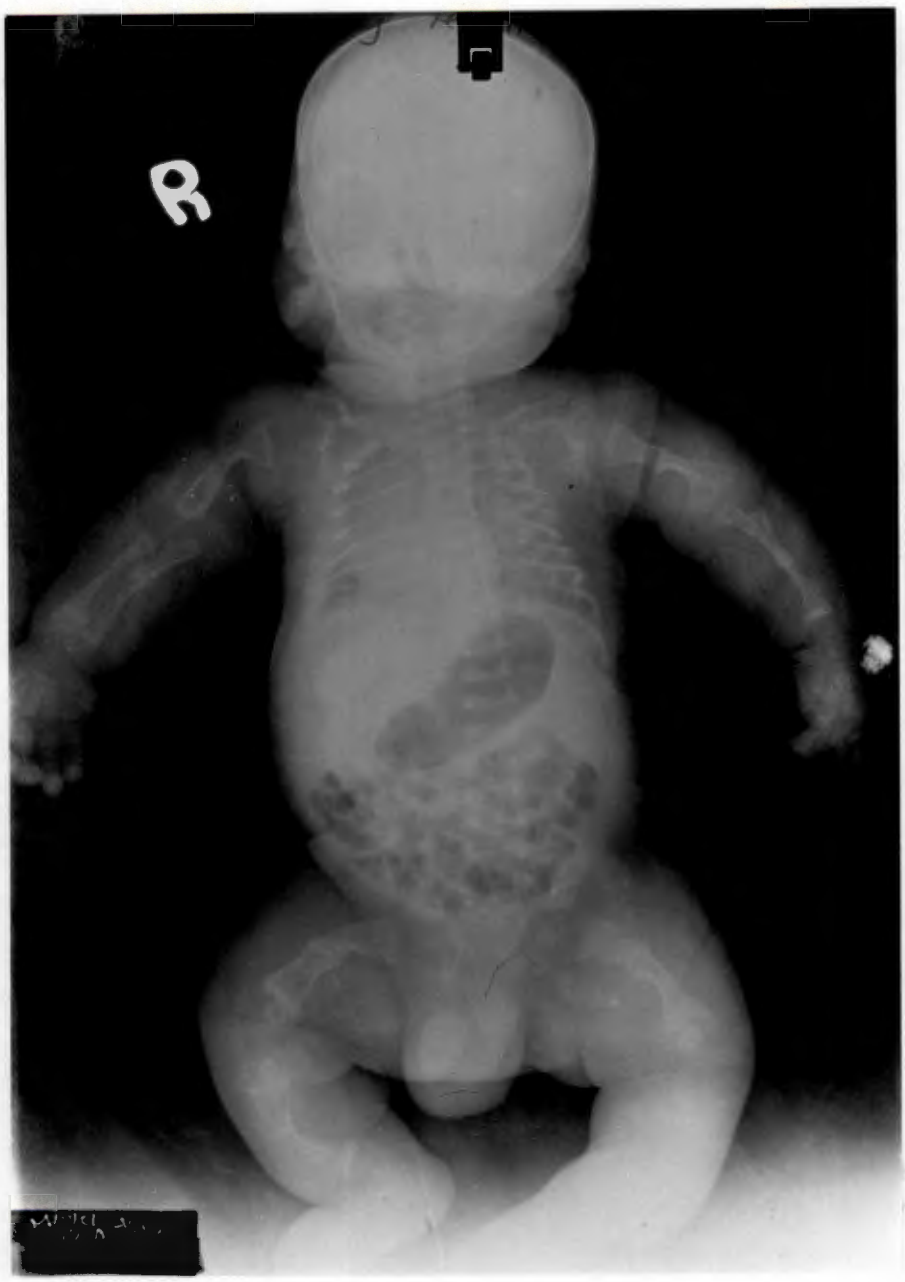

Fig. 17-2: Radiograph of a neonate with the presumptive diagnosis of lethal OI: thin ribs and "apple-core" femora are evident.

17.3 PFEIFFER SYNDROME - ACROCEPHALOSYNDACTYLY TYPE V

A Chinese boy, aged two years was the second son of normal, non-consanguineous parents. He presented at birth with marked brachycephaly and facial disproportion, a depressed nasal bridge, choanal atresia, hypertelorism, maxillary hypoplasia and prognathism. There was prominant broadening of his thumbs and toes, with radio-humeral synostosis and hypoplasia of the deltoid muscles. Psychomotor development had been satisfactory. Cosmetic craniofacial surgery was undertaken at one year and ray excisions of the second toes were performed at this stage. Radiographs demonstrated cranio-synostoses of the sagittal and left lambdoid sutures, a kleeblatschädel anomaly and radially deviated thumbs with broad distal phalanges. Fig. 17-3 depicts this child post surgery, with his elder, unaffected brother.

The combination of features described here closely fit the Pfeiffer form of acrocephalosyndactyly (Martsolf et al, 1971). This rare condition is clinically distinct from other similar craniosynostosis syndromes (Apert, Saethre-Chotzen), has an AD mode of inheritance and shows phenotypic variability (Gorlin et al, 1976a). The hypoplasia of the deltoid muscles with consequent limitation of abduction of the arms has not been documented previously and no description of the facial features in an affected oriental child could be found in the literature.

Fig. 17-3: A Chinese boy with Pfeiffer syndrome accompanied by his elder brother.

17.4 EEC SYNDROME WITH NORMAL LIP AND PALATE

Six members of a four generation Creole family presented with varying degrees of split-hand/split-foot anomaly and ectodermal dysplasia. The pedigree of this kindred (Fig. 17-4) demonstrated clear evidence of AD inhertance with a single instance of non-penetrance (Pedigree # III-2). The split-hand/split-foot deformities ranged from virtual normality to severe tetramelic deficiencies; the ectodermal dysplasia manifested as hypotrichosis, and imperfect dentition.

The clinical spectrum of abnormalities in the affected individuals is summarised in Table 17-II and further portrayed in Figs. 17-5 and 17-6 and 17-7. There was no clefting of the lip or palate in any family member and no clinical evidence for lacrimal duct abnormalities, mental retardation or urogenital problems.

Radiographic studies were undertaken on the proband (Pedigree no IV-1). The forearms showed severe, bilaterally symmetrical radial ray deformities with monodactyly (Fig. 17-8). Films of the lower limbs demonstrated severe reduction defects of the tibiae, a single metatarsus on each side and monodactyly. The symmetry and severity of these lower limb malformations is depicted in Fig. 17-9.

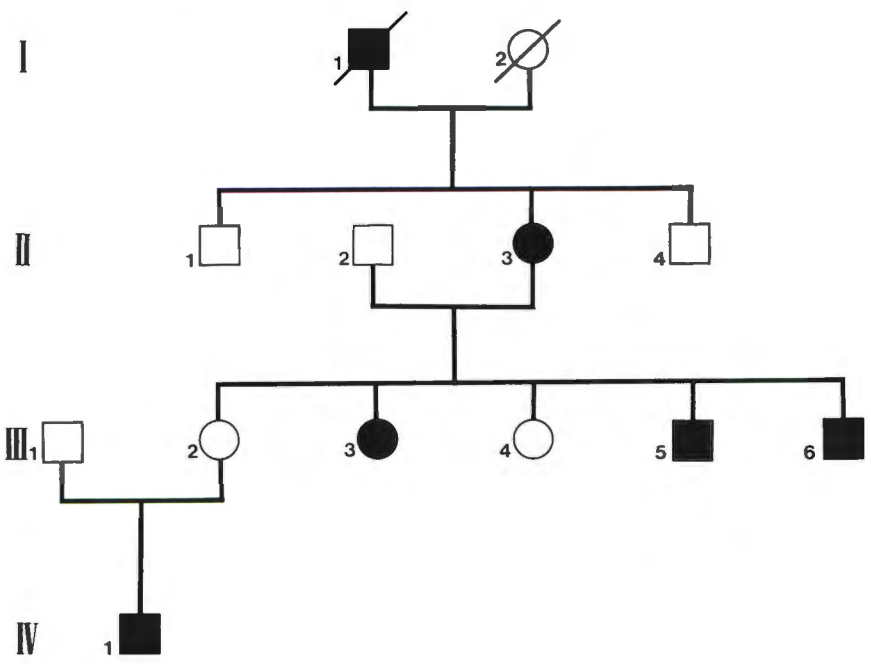

Fig. 17-4: The pedigree of a kindred with an EEC syndrome.

Pedigree No.	II-3	III-3	III-5	III-6	IV-1
Figure	17-6	17-5	17-6	17-6	17-7
Hair	Thin	Sparse	Sparse	Sparse,	Thin, sparse
Skin	N	N	N	N	N/Dry
Left hand	N	5th digit campto-dactyly.	Split	Monodactyly	Monodactyly
Right hand	Split	5th digit campto-dactyly.	Split	Split	Monodactyly
Left foot	Split	N	Mono-dactyly.	Mono-dactyly with absent tibiae.	Monodactyly with pro-truberant & dyplastic tibia and fibula.
Right foot	Split	N	Mono-dactyly.	Split	As above
Teeth	Edentu-lous	N	Only 4 hypo-plastic teeth in total	Only 4 poorly developed premolars in total.	A total of 8 teeth, pointed and imperfectly developed.
Lip/ Palate	N	N	N	N	N

Table 17-II: A summary of the clinical findings in 5 relatives with a form of EEC syndrome. The pedigree numbers correlate with Fig. 17-4. (N = normal)

Fig. 17-5: EEC syndrome: Two affected individuals [IV-1 on left; III-3 on right] demonstrate the range of phenotypic expression for 'ectrodactyly' in this family.

Fig. 17-6: EEC syndrome: The facial features and range of hand malformations in individuals III-4, III-5 and II-3 (Left to Right).

Fig. 17-7: The proband (IV-1) with severe, tetramelic malformations and ectodermal dysplasia.

Fig. 17-8: Radiograph of the forearm of IV-1: The radial malformation and monodactyly is evident.

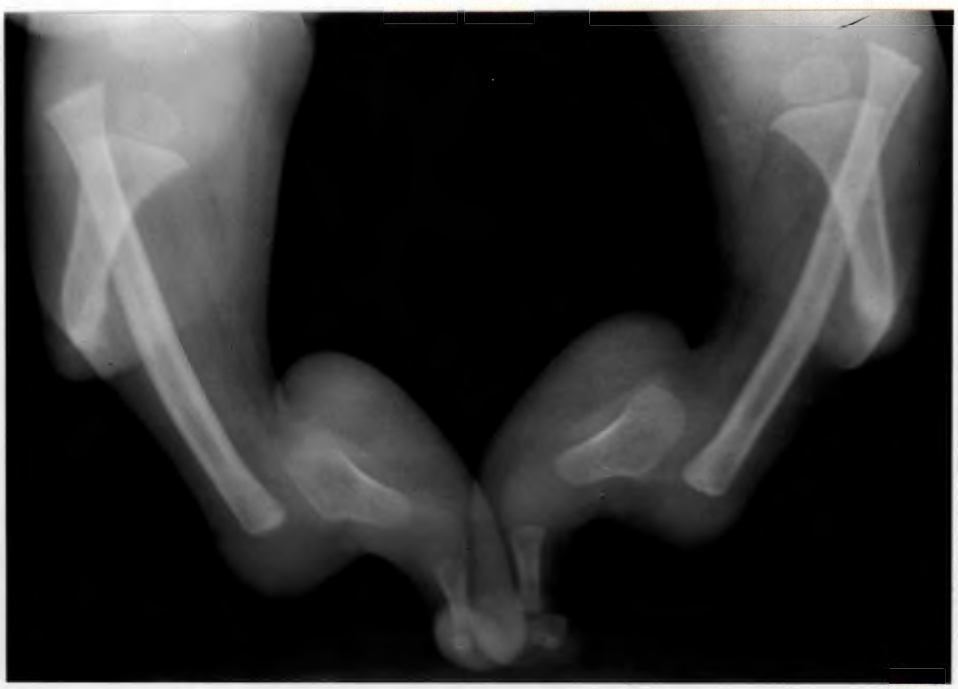

Fig. 17-9: Radiograph of the lower limbs of IV-I: Bilateral, severe malformations are present.

The EEC syndrome comprises ectrodactyly, ectodermal dysplasia (sparse hair, hypodontia, hypohidrosis, lacrimal duct anomalies) and clefting of the lip and/or palate (Preus and Fraser, 1973). A wide range of phenotypic expressivity is well-recognised and difficulties exist in establishing syndromic boundaries (Küster et al, 1985). It has been proposed that separate status for the condition of ectrodactyly and ectodermal dysplasia with normal lip and palate is justified. However, a paucity of well-documented, affected families has failed to substantiate the separate existence of this entity (Richieri-Costa et al, 1986).

The Mauritian family presents 6 members (five examined and one (I-1) described by independent sources) with varying degrees of split-hands/split-feet and ectodermal dysplasia. Notwithstanding the significant number of affected individuals, no person had clefting of the lip or palate. On this basis, separate syndromic status for an ectodermal dysplasia - ectrodactyly syndrome with normal lip and palate seems likely.

It is most likely that the EEC syndrome, with and without a normal lip and palate, as well as conditions such as the Adams-Oliver syndrome (Bonafede and Beighton, 1979) and the odontotrichomelic syndrome (Pinheiro and Freire-Maia, 1980) form a "family" of similar but distinct genetic disorders with many areas of phenotypic overlap.

17.5 FIBROUS DYSPLASIA OSSIFICANS PROGRESSIVA

A pre-adolescent boy had the characteristic ectopic calcification of this rare AD disorder. Lateral radiographs (Fig. 17-10) showed sheets of calcified tissue beneath the surface of the skin in the neck and upper back. The family history was negative and this boy was presumed to represent a fresh dominant mutation. Variable phenotypic expression makes prediction of individual prognosis difficult but in general the natural history is one of erratic but progressive disability (Conner, 1983).

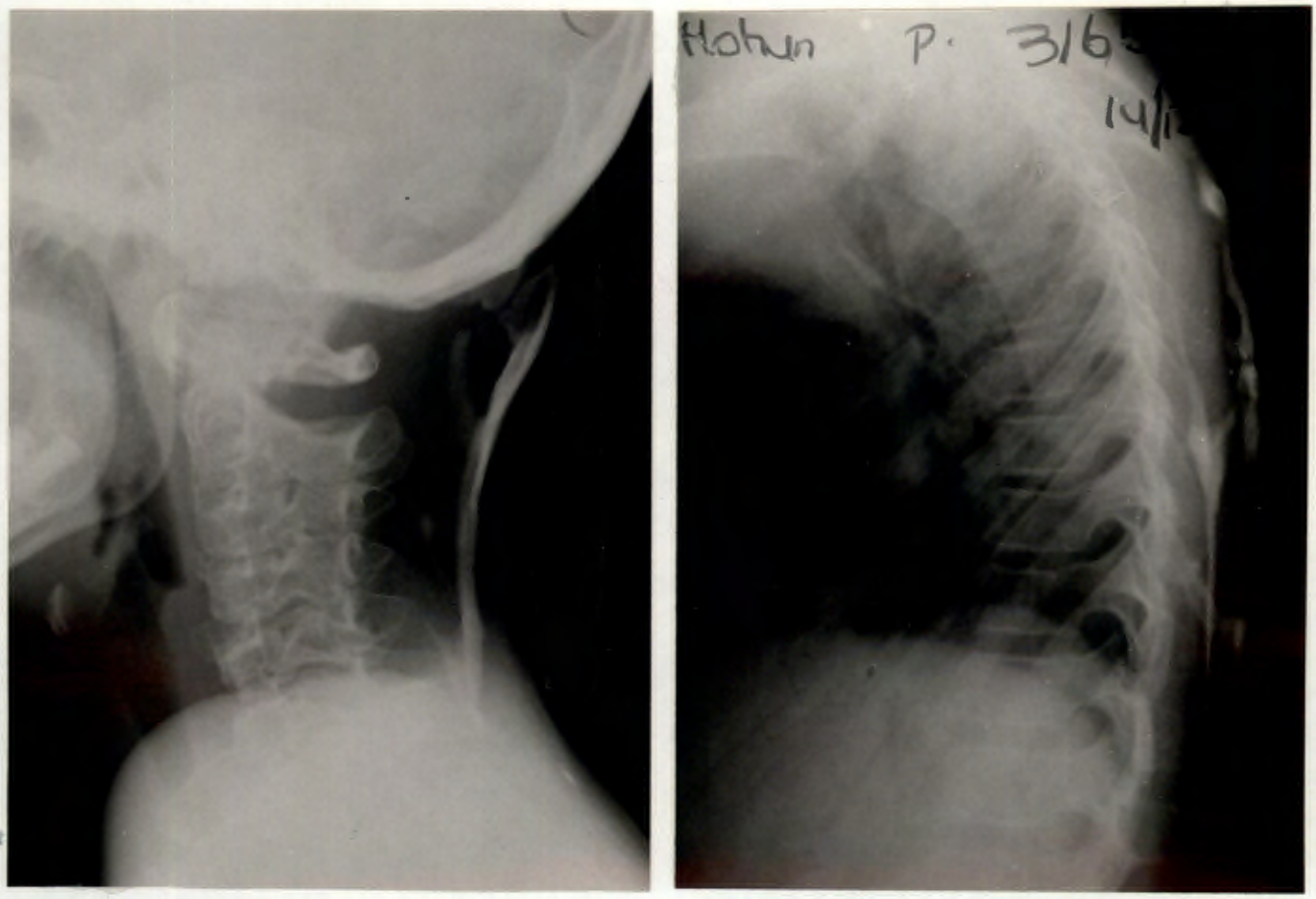

Fig. 17-10: Fibrous dysplasia ossificans progressiva: Lateral radiographs of the neck and chest show the soft tissue calcification.

17.6 PYKNODYSOSTOSIS

Two Muslim brothers, aged 45 years and 26 years presented with the problem of short stature. Their parents were first cousins and they had 8 normal brothers and sisters.

The two affected males had a height of 131 cm and 138 cm respectively and bore a strong phenotypic resemblance to each other (Fig. 17-11). The clinical features included a patent anterior fontanelle, prominence of the frontal bones, malar and mandibular hypoplasia, a deeply grooved palate with double-row dentition, brachydactyly and deformity of the lower limbs due to multiple fractures.

Radiographic features in both individuals included osteosclerosis of the entire skeleton, spool-shaped vertebral bodies, an obtuse mandibular angle, a J-shaped sella turcica and open sagittal sutures (Fig. 17-12). Healed fractures were evident and radiographs of the hands demonstrated brachydactyly and acro-osteolysis.

Fig. 17-11: Pyknodysostosis: Two brothers demonstrate the features of an open anterior fontanelle, malar hypoplasia and frontal bossing.

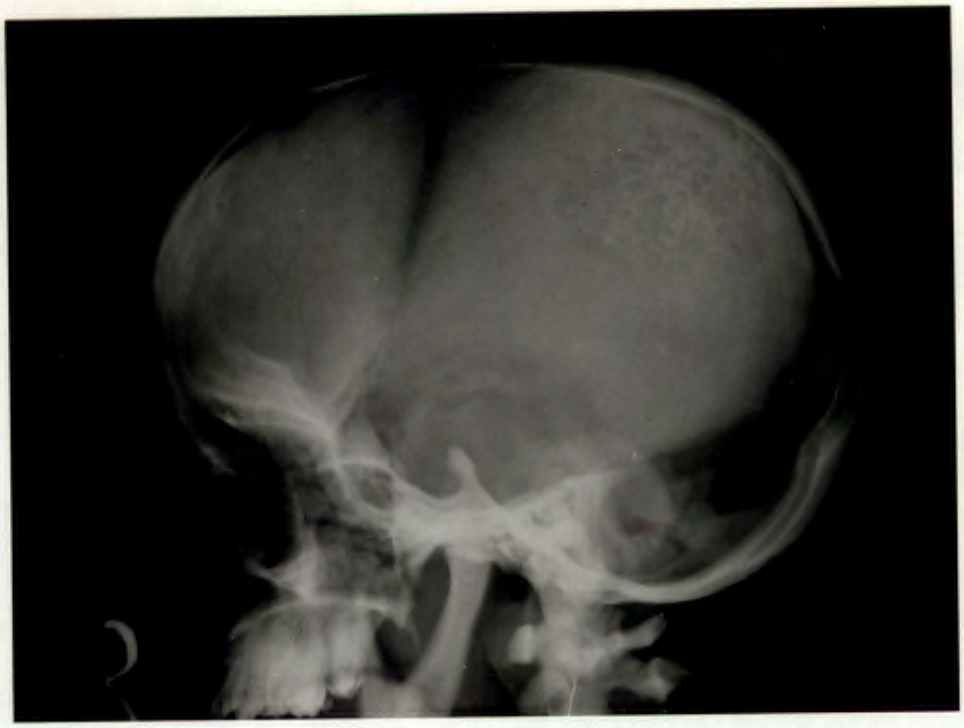

Fig. 17-12: Lateral radiograph of the skull in pyknodysostosis: The osteosclerosis, open sutures, small mandibular angle and prominence of the occipital and frontal bones is evident.

Pyknodysostosis is a rare sclerosing bone disorder with abnormalities of the skull, maxilla and phalanges, dwarfism and bone fragility. Approximately 150 cases have been documented in a wide range of geographical and ethnic settings (Beighton and Cremin, 1980).

The two Mauritian Muslim males have the classical clinical and radiographic features of pyknodysostosis. The closely consanguineous union in this family is in keeping with the well-documented AR mode of inheritance for the disorder.

Recently, further evidence of pyknodysostosis in the Muslim community has been provided by a report of an affected child of consanguineous parents belonging to this religious group (Kumar et al, 1988).

17.7 SPONDYLOCOSTAL DYSOSTOSIS

A Hindu woman, aged 23 years, presented with severe abnormalities of the entire spine. The cervical region was rigid, no movement of the head was possible, the hair line was low and fixation of the temporo mandibular joint limited mouth-opening to one centimetre. There was a kyphoscoliosis of the thoraco-lumbar spine and both scapulae were elevated and fixed. Arm span exceeded height by 4 cm. The natural history was poorly documented but the spinal changes appeared to have been present in infancy and had remained unchanged through adolescence. There were no other joint problems and no record of systemic illness. No precipitating events were known and there was no pertinent family history. Secondary problems included difficulty with mastication and a reactive depression.

Radiographic studies demonstrated multiple hemivertebrae with abnormalities of the ribs in number and form (Fig. 17-13). Bony ankylosis extended throughout the vertebral column and was particularly evident in the lumbar region where total fusion had occurred.

Fusion of the vertebral bodies can follow trauma or infection, but also occur as a congenital abnormality, either sporadically or associated with chromosomal and genetic disorders (Kozlowski and Beighton, 1984). For the young woman described here, the additional presence of multiple hemi-vertebrae, favours a congenital rather than an acquired aetiology. Two entities deserve consideration in the differentiated diagnosis.

The **Klippel-Feil Syndrome** is almost certainly a heterogeneous group of disorders that share, to varying degrees, the cardinal features of cervical spine fusion with malsegmentation of the vertebrae. Extention to other parts of the vertebral column has been documented and classifications based on severity and site have been suggested (Gunderson et al, 1967). Secondary effects include

the clinical stigmata of a low hair line, limitation of neck movement, kyphoscoliosis and Sprengel shoulder. Rib changes may be evident on chest radiographs (Shoul and Ritvo, 1952). If the patient described here were to be categorised within the phenotypic spectrum of the Klippel-Feil syndrome, she would be as severely affected as any example yet documented.

Fig. 17-13: A radiograph of the chest demonstrates multiple hemivertebrae, spinal fusion and rib abnormalities of form and number.

Spondylocostal dysostosis (spondylo-thoracic dysplasia) is an AR condition with the major features of a short neck and thorax, limitation of spinal mobility, kyphoscoliosis, vertebral anomalies including hemivertebrae and vertebral fusions, and rib abnormalities of form and number (Castroviejo et al, 1973). Severe spinal ankylosis is not commonly documented for this condition and emphasis is generally placed on the short stature (Silengo et al, 1978). There are, however, sufficient criteria for a diagnosis of spondylocostal dysostosis in this Mauritian girl. Her phenotype exemplifies the similarities between this syndrome and the severe form of Klippel-Feil anomaly.

17.8 BRACHYDACTYLY, DWARFISM AND HIP DYSPLASIA

A 46 year old male, with a non-contributory family history presented with the following clinical abnormalities of the skeleton: dwarfism (height 124 cm; span 123 cm), marked brachydactyly, stiffness of all limb joints, fixed flexion of the hips and limited spinal movements. Additional phenotypic features included coarse facial features (Fig. 17-14), mild mental retardation, nasal speech, a barrel chest and an aortic ejection murmur. There was no clinical enlargement of the liver and spleen, his vision was normal and his corneae were clear on fundoscopic examination.

Radiographic changes in the spine and long bones were mild and non-specific. Films of the hands (Fig. 17-15) showed marked brachydactyly with narrowing of the metacarpal shafts. The femoral capital epiphyses were very dysplastic and fragmented (Fig. 17-16).

Fig. 17-14: An individual with brachydactyly, coarse facial features and dwarfism.

Fig. 17-15: Radiograph of the hands: Brachydactyly with narrowing of the metacarpal shafts is shown.

Fig. 17-16: Radiograph of the pelvis: Gross destruction of the femoral epiphyses and flaring of the iliac wings is demonstrated.

The coarse facies and skeletal changes found in this individual, indicate a possible biochemical abnormality of the lysosomal enzyme system. This large group of disorders is notoriously heterogeneous and clinical parameters are seldom pathognomonic (Spranger, 1987). The sophisticated investigations required for a precise diagnosis are not presently available on Mauritius. Phenotypically, however, there were striking similarities to previously reported patients with mucolipidosis Type III (Stein et al, 1974) and this disorder is suggested as a "best-fit" diagnosis for this syndrome of brachydactyly, dwarfism and hip destruction. Mucopolysaccharidosis type VI is worthy of consideration, but unlikely in the absence of visceral organomegaly or ocular pathology (Gorlin et al, 1976b).

17.9 ENCHONDROMATOSIS WITH DWARFISM AND DEAFNESS

A girl of Hindu stock, born in 1977, was the eighth of ten normal siblings. There was no family history of deafness or skeletal abnormality and her parents were unaware of any consanguinity. Limb length discrepancy, first noticed at birth, became pronounced during early childhood. A fractured femur at the age of three years was managed conservatively and there were no sequelae. Bilateral sensori-neural deafness precluded the development of speech. At the age of seven years she underwent enucleation of her left eye for a "cancer"; no information pertaining to the exact pathology was available and no medical records could be traced.

Clinical examination at age 10 years revealed a severely dwarfed, pre-pubertal female of height 110 cm (< 3rd centile for age) and head circumference 51 cm (25th centile) with profound deafness and absent speech. The gross physical abnormalities included a marked lumbar lordosis, asymmetrical shortening of the long bones with maximal involvement of the left arm and right leg, thickening of the metaphyses most evident at the wrists and a left genu valgum (Fig. 17-17). The hands and feet were essentially normal. No abnormalities were detected in any other system and intellectual function was normal.

The major radiographic feature was the presence of widespread enchondromata. The pelvis showed gross enchondromatous changes in the acetabulae and streaky translucencies in both iliac crests (Fig. 17-18). In the upper femora, similar abnormalities containing variable but often extensive calcification, were associated with changes to the femoral necks, capital epiphyses and hip joint margins.

In the long bones there was gross enchondromatous involvement of the metaphyses and diaphyses (Fig. 17-19) with associated asymmetrical limb shortening (Fig. 17-20). In the hand there was minor involvment of the short tubular bones (Fig. 17-21).

The skull radiographs were normal. The vertebral bodies had irregular end plates together with some degree of flattening. In the first thoracic vertebra there was a spina bifida occulta, with defective development of the left half of the neural arch.

Fig. 17-17: A young girl with dwarfism and deafness: These photographs show asymmetry of the limbs, widening of the knee joints and wrists, a left genu valgum, facial asymmetry and a spinal lordosis.

Fig. 17-18: Radiograph of the pelvis with gross enchondromatous changes.

Fig. 17-19:
Radiograph of the upper limbs: Enchondromata extend into the shaft of the humerus.

Fig. 17-20:
Radiograph of the lower limb: Gross enchondromatous involvement of the metaphyses and diaphyses is demonstrated.

Fig. 17-21:
Radiograph of the hand: Enchondromatous involvement of the tubular bones.

This girl has marked limb asymmetry and malalignment due to extensive enchondromata of the long bones. Dwarfism and sensori-neural deafness were additional concomitants; the former is exceptionally rare in the enchondromatoses and the latter has not been previously recorded (Mainzer et al, 1971). Spranger et al, (1978) reviewed the literature and presented a classification of six types of enchondromatosis of which the last three categories all mention some degree of spinal involvement including irregular dysplasia of the vertebral bodies. The additional features of marked dwarfism and profound deafness in the Mauritian girl, present difficulties in assignation to any group and it seems likely that she has a previously undocumented entity.

CHAPTER 18

GENETIC NEUROMUSCULAR DISORDERS:

FINDINGS AND DISCUSSION

8.1 INTRODUCTION

Genetic diseases of the neuromuscular system have a history that is fraught with nosological confusion and as a group they have confounded many attempts at a satisfactory classification. Clinical delineation is complicated by the heterogeneity, variable expressivity and unpredictable natural history of many of these disorders. Recent advances in histopathology and electromyography have proven to be useful diagnostic tools and classifications of increasing accuracy have evolved (Ionasescu and Zellweger, 1983). The study of the molecular nature of neuromuscular diseases holds the promise of theoretical and practical solutions for the future.

In the absence of sophisticated technology for this study, genetic disorders of neuromuscular origin on Mauritius were divided into three broad groups: the myopathies; the spinal muscular atrophies (SMA) and hereditary neuropathies; and the inherited ataxias and spastic paraplegias. Further differentiation was made on a basis of the clinical findings, natural history and the pattern of inheritance. The inborn errors of metabolism and those conditions with co-existing mental handicap are not included in this chapter.

During the Mauritian survey, 28 individuals with genetic neuromuscular disease were documented. The findings are summarised in Table 18-I and discussion follows.

CLINICAL DIAGNOSIS	INHERITANCE	TOTAL	NO OF FAMILIES
Myopathies:			
Duchenne muscular dystrophy	XL	13	7
Becker muscular dystrophy	XL	3	2
Limb girdle muscular dystrophy	AR	2	2
Unclassified muscular dystrophy	?AR/XL	2	1
Distal myopathy	AD	3	1
Spinal Muscular Atrophies (SMA) and Hereditary Neuropathies			
Proximal SMA (type III)	AR	3	2
Inherited Ataxias and Spastic Paraplegias:			
Spino-cerebellar ataxia	AR	1	1
Sjögren-Larsson syndrome	AR	1	1
TOTAL		28	17

Table 18-I: An analysis of neuromuscular genetic disease in 28 individuals.

18.2 MUSCULAR DISORDERS ON MAURITIUS

18.2.1 Duchenne Muscular Dystrophy (DMD)

DMD, a common genetic disorder with a general incidence of about 1/4,000 live male births (Emery, 1987), was encountered in 13 Mauritian boys from 7 families. Their clinical picture and the course of their disease was typical for DMD. Six of the 7 affected families resided in the most Southern regions of the Island, however, no common ancestry could be determined and the geographical clustering of the disorder in this part of Mauritius could not be explained. Almost half of the probands were considered to be new mutations, a finding in keeping with other studies (Moser, 1984).

The development of molecular services for carrier detection using probes for the Xp21 region will facilitate diagnostic tests of 95-99% accuracy for most kindreds (Goldblatt et al, 1987). With regard to the Mauritian community, blood samples are readily transportable to specialised laboratories abroad and informative results will significantly enhance genetic counselling. In two individuals, documented in this chapter, the diagnosis was confirmed in the Department of Human Genetics, University of Cape Town, using molecular techniques.

18.2.2 Becker Muscular Dystrophy

Becker muscular dystrophy, which is approximately 10 times less frequent than Duchenne muscular dystrophy, has been described as "a slow motion copy of DMD" (Ionasescu and Zellweger, 1983). It was encountered in a Creole male, aged

23 years, who presented with the classical clinical course, and in two Chinese brothers aged 6 years and 5 years. In the latter siblings, the diagnosis had been made following a muscle biopsy performed in the United Kingdom as part of an investigation into their developmental delay. Both these boys had mild mental retardation.

18.2.3 Limb Girdle Muscular Dystrophy (LGMD)

LGMD was found in a brother and sister, the parents of whom were first cousins. Although the boy was more severely affected, their clinical course had followed the classical pattern for this disorder.

Proximal muscle weakness is the clinical expression of a heterogeneous group of conditions and genetic variants of spinal muscular atrophy can simulate limb girdle dystrophy. Clinical separation of LGMD from proximal SMA can be difficult without electromyography and muscle histology.

18.2.4 Unclassified Muscular Dystrophy

An unusual pedigree of a family in which two male cousins were affected by muscular dystrophy is presented in Fig 18-1. Close parental consanguinity is evident and, in the absence of any other affected relatives, autosomal recessive inheritance is highly probable. However, the boys, aged 9 years and 12 years, had a clinical picture and natural history that fitted the pattern of DMD. X-linked inheritance is still genealogically feasible, albeit in the face of

greater odds for autosomal recessive transmission. Here is a *scenario par excellence*, where molecular technology could accurately resolve the diagnostic dilemma and facilitate confident and informed genetic counselling for the extended family. (The outcome of the molecular investigation is described in Appendix F.)

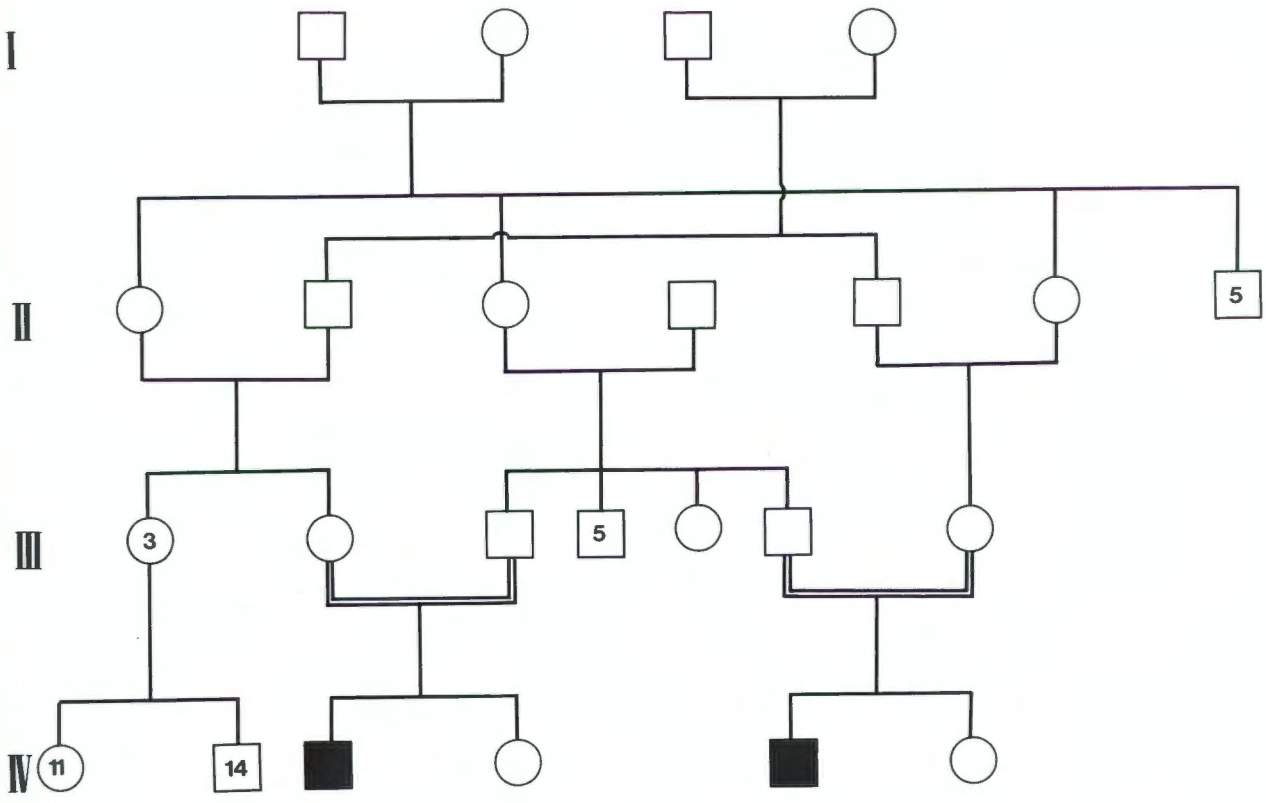

Fig. 18-1: A pedigree of a consanguineous family showing two male cousins with muscular dystrophy.

18.3 SPINAL MUSCULAR ATROPHIES AND THE HEREDITARY NEUROPATHIES

18.3.1 Spinal Muscular Atrophy (SMA)

The spinal muscular atrophies are characterised by progressive neuronal degeneration of the anterior horn cells in the spinal cord and disappearance of the motor nuclei in the brain stem. AD, AR and XL forms have been described and further sub-classification has been formulated in terms of the clinical course and the results of electromyographic and histopathological studies.

Three individuals had the classical clinical features and natural history of proximal spinal muscular atrophy (PSMA) type III. AR inheritance was likely in all instances as two of the three were siblings and the third, a female, had consanguineous parents.

PSMA is the most frequent form of spinal muscular atrophy, representing over 80% of all SMA's. No other types were detected during the Mauritian study. It is entirely feasible that no individuals with juvenile or early fatal forms were alive during the period of study and that past cases had remained undiagnosed and thus unreported. Chronic infantile forms of PSMA are also clinically difficult to detect in the later stages of the disease and may have been incorrectly diagnosed. A family with the dominant form would, however, have been less likely to escape ascertainment in the Mauritian survey. As no cases were detected, it is likely that this gene is not present on the Island.

A report by Pascalet-Guiden et al (1984), concerning a cluster of 19 persons with acute infantile SMA (type I) belonging to 13 sibships on the neighbouring Island of Réunion is of interest and relevance. This high incidence among the 'Petit Blancs' is explained on the basis of their geographical isolation, consanguinity and a founder effect traced back to 1642. Mauritius has origins and a history that parallels Réunion and the two islands are a mere 100 nautical miles apart. The virtual absence of this disorder on Mauritius compared with the very high frequency on Réunion, is a clear example of the rôles of the founder effect and subsequent endogamy in the determination of the geographic distribution of genetic disease in isolated communities.

18.3.2 Hereditary Neuropathies

In the realm of genetics and neurology, the hereditary neuropathies are considered to be relatively common. Indeed, a prevalence of 1 in 9,000 Swedish school children has been quoted by Hagberg and Westerberg (1983). In one study, hereditary neuropathies were found in 63 out of 80 children presenting with distal weakness (Hagberg and Westerberg, 1983a).

No examples of hereditary neuropathies were encountered on the Island of Mauritius. The reasons for this surprising finding are not clear as families with AD disorders such as Charcot-Marie-Tooth disease are unlikely to have escaped the ascertainment protocols used in this survey. Sporadic cases or rare recessive forms may have been missed, unreported or misdiagnosed. However, it is possible that the abnormal genes are simply not present on the Island.

18.4 INHERITED ATAXIAS AND SPASTIC PARAPLEGIAS

The classification of the inherited ataxias has been a matter of dispute and some taxonomists suggest that they should not be classified at all! The generally accepted prevalence of the inherited ataxias is less than 6 cases per 10,000 and at least 60 types are mentioned in the literature. The prevalence is highest for communities characterised by isolation and inbreeding (Ionasescu and Zellweger, 1983a).

Two disorders which belong to the category of inherited ataxias and spastic paraplegias were documented on Mauritius and are described in the concluding paragraphs of this chapter. Persons with associated mental retardation (eg. Behr syndrome) have been discussed in Section IV of this thesis.

18.4.1 Spino-Cerebellar Ataxia

A single instance of spino-cerebellar ataxia was seen in a woman aged 25 years. Onset occurred in late adolescence and marked cerebellar and long tract signs were present. The family history was non-contributory and in the absence of any underlying cause, it is probable that she had a form of AR spinocerebellar ataxia.

18.4.2 The Sjögren-Larsson Syndrome

An Indian male aged 23 years, was the 2nd of three sons born to closely consanguineous parents. He presented at birth with dry, ichthyotic skin which became increasingly pachydermatous with time. The face, palms and soles were spared (Fig. 18.2). At the age of six years, without any predisposing event or illness, he developed spasticity of the lower limbs. Both legs were equally affected but there were no sensory or cerebellar deficits. The arms were spared and there had been no progression of his neurological status since childhood. At the time of examination, he had a height of 180 cm and apart from the skin changes (Fig. 18-3, Fig. 18-4) and spasticity of the lower limbs he was clinically well. Features of special significance were his normal hair, normal retina and unimpaired renal function. His level of intelligence was average and he had no speech defects. He completed school without difficulty and was capable of gainful employment. There was no relevant family history.

Fig. 18-2:

A male of normal stature and intelligence with ichthyosis and spastic paraplegia.

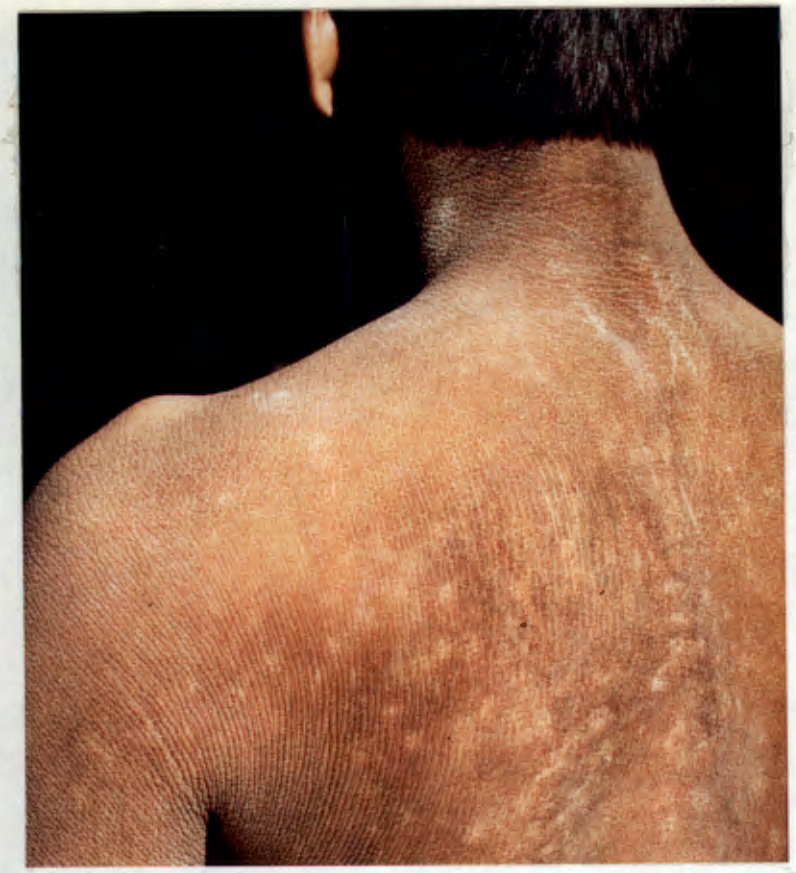

Fig. 18-3:
Ichthyosis in an adult male with Sjögren-Larsson syndrome.

Fig. 18-4:
The individual portrayed in Fig. 18-2: the skin changes spare the face.

The Sjögren-Larsson syndrome (SLS) is characterised by the cardinal features of congenital icthyosis, spastic diplegia or tetraplegia and mental retardation (Jagell and Liden, 1982). This AR entity has a high prevalence in certain parts of Sweden where the carrier rate is approximately 1 in 50 (Jagell et al, 1981). In a comprehensive study of 35 Swedish patients, a uniform phenotype was documented: generalised icthyosis less pronounced on the face, spastic diplegia usually noticed before 3 years of age and mental retardation obvious during early childhood (Jagell et al, 1981).

The Mauritian male, described above, presents with a dermatological picture and neurological signs compatable with SLS. The close parental consanguinity is evidence for AR inheritance of his condition. However, his normal mental status, late onset of paraplegia, tall stature and normal fundoscopic appearances are unusual for this syndrome.

A wide phenotypic spectrum for SLS has been documented by various authors (Rayner et al, 1978) including late onset of spasticity and normal intelligence (Ionasescu et al, 1973). Furthermore, intra-familial variation has been encountered (Selmanowitz and Porter, 1967). It thus appears that the phenotypic range for the diagnosis of SLS might well embrace this patient.

A single case report of a six year old Indian girl with the classic features of the Sjögren-Larsson syndrome born to consanguineous parents has appeared in the Indian medical literature (Maiya, 1977). However, no other cases of SLS were found amongst the Hindu community of Mauritius and the gene frequency is presumably of a low order in this group.

CHAPTER 19

GENETIC DISORDERS OF THE SKIN AND EXOCRINE GLANDS: FINDINGS AND DISCUSSION

19.1 INTRODUCTION

A wide range of genetic conditions manifest with readily detectable clinical changes to the skin. These dermatological findings may represent the sole manifestation of an abnormal gene, as in ichthyosis, or they may be part of an ectodermal dysplasia or neurocutaneous syndrome with additional underlying pathology.

Several examples of handicapping genetic disorders with skin changes have been discussed in the preceding chapters of this thesis. In this chapter, attention is given to those inherited conditions where the dermatological effects are considered to have a predominant clinical and functional impact. However, it is accepted that classification on such loose criteria is open to debate; the Sjögren-Larsson syndrome or the epidermal naevus syndrome are obvious examples where multisystem pathology denies satisfactory classification.

DISORDER	INHERITANCE	TOTAL
Hypohydrotic ectodermal dysplasia	XL/AR	2 (1 family)
Lamellar ichthyosis	XL/AR	1
Ichthyosis	AR	1
Alopecia, cataracts and sclero-dactyly syndrome	AR	1
Neurofibromatosis	AD	1
Epidermal naevus syndrome	UN	1

Table 19-I: Genetic disorders of the skin and exocrine glands.

19.2 HYPOHIDROTIC ECTODERMAL DYSPLASIA SYNDROME (HED)

A male, aged 4 years, and his sister, aged ten years, were the only progeny of consanguineous second-cousin parents. The boy presented with a single pointed tooth, sparse thin hair, smooth skin and anhidrosis with severe hyperthermia. Vision, intelligence and the locomotor system were all normal. His facial features are depicted in Fig. 19-1.

The proband's sister had minimal hypohidrosis, her teeth were pearly grey in colour and her hair was normal. No other affected individuals were reported in the maternal or paternal sides of the pedigree.

Fig. 19-1: Hypohidrotic ectodermal dysplasia: The facial features of a four year old boy with anhidrosis, absent teeth and sparse hair.

Hypohidrotic ectodermal dysplasia (HED) is genetically heterogeneous, and X-linked, AR and AD types have been described (Clarke, 1987). The X-linked form is the most common variety and in this entity, about 70% of heterozygous females have mild clinical manifestations (Pinheiro and Freire-Maia, 1979).

Two points are illustrated by the description of this Mauritian case. Anhidrosis is a crippling handicap and potentially lethal in the Island's hot and humid summers. In the X-linked form of HED, even the heterozygous female is at risk of developing the infections, hyperpyrexia, cot deaths and childhood mortality associated with this disorder. It is clear that certain environmental climates will be disadvantageous to the gene carrier and could limit the prevalence of the condition.

In this family, the presence of parental consanguinity complicates accurate counselling as both the AR and XL forms of HED are compatable with the genealogical information and clinical picture. Recently Clarke et al (1987) have localised the HED gene to the centromeric region of the X chromosome. If heterogeneity can be excluded for the XL type, linkage analysis could provide a molecular diagnosis for this family and facilitate a greater accuracy in counselling.

.3 ICHTHYOSIS

The ichthyoses are a heterogeneous group of generalised, persistent, scaling disorders (the term derives from a similarity to fish skin). The dermal abnormalities are occasionally localised and in exceptional cases accompanied by erythema. Most of the ichthyoses are genetic and AD, AR and XL types have been recognised (Wells and Kerr, 1966).

Two sporadic individuals with different forms of ichthyosis were ascertained on Mauritius. As there were no geneological clues as to their inheritance pattern, diagnostic categorisation was attempted on clinical grounds.

The individual portrayed in Fig. 19.2 has the features of a rare autosomal recessive entity, **lamellar ichthyosis.** Due to the severe involvement of this boy's body and face, he had been unable to attend school and his psychological development was retarded. The secondary handicap which can arise from certain inherited dermatological conditions is amply illustrated by this case.

The skin features of a boy, aged 8 years, considered to have **ichthyosiform erythroderma** are depicted in Fig. 19-3. There was no parental consanguinity or relevant family history. Several disorders are included in the literature under this term (Ebling et al, 1986), and the confusion makes accurate genetic counselling impossible for this individual. The sparing of his face, palms and soles are ultimately unhelpful as phenotypic clues to further syndromic categorisation.

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Fig. 19-2:

Congenital lamellar ichthyosis.

Fig. 19-3:

Congenital ichthyosis, with sparing of the face, palm and soles.

19.4 ALOPECIA, CATARACTS AND SCLERODACTYLY SYNDROME

A woman with total alopecia, congenital cataracts and dermatological changes to the tips of her fingers and toes was encountered on Mauritius. Affected relatives with this unusual AR condition live on the Island of Rodrigues. A full discussion of this entity is provided in Chapter 22, but is mentioned here for completeness.

19.5 NEUROFIBROMATOSIS (NF)

A male, aged 24 years, had multiple large café-au-lait macules with generalised cutaneous neurofibromas (Fig. 19-4). In addition he had a cervicothoracic kyphoscoliosis and Lisch nodules in his irides. He was the only affected offspring of Indian, Creole and Chinese grandparents and represented a new mutation of the NF gene.

Neurofibromatosis is a common AD disorder which has a wide range of phenotypic expression. A prevalence of about 1 in 3000 has been quoted (Crowe et al, 1956) and the absence of any large AD kindred with NF on Mauritius is thus surprising. Incomplete ascertainment of affected cases could be the reason for this low prevalence in the present survey; the clinical manifestations of NF can be mild and in these circumstances the condition could escape recognition and referral.

Fig. 19-4: Neurofibromatosis in a man of mixed Creole-Chinese origin: Pigmented macules, neurofibromata and a scoliosis are evident.

19.6 EPIDERMAL NAEVUS SYNDROME

A Hindu boy, aged 17 years, was the only son of unaffected non-consanguineous parents. The family history was unremarkable. He presented with generalised skin changes, mental retardation and left-sided hemi-atrophy which included the face and testis (Fig. 19-5).

Fig. 19-5:

A 17 year old youth with right-sided hemi-atrophy, skin changes and mental retardation.

His height was 143 cm (less than the 3rd percentile) and his head circumference was 54 cm (25th percentile). His right arm and right leg were 3 cm longer than his left-sided limbs. A secondary scoliosis discrepancy in size was present in the thoracic and lumbar regions (Fig. 19-6).

Fig. 19-6:
A scoliosis, secondary to hemi-atrophy, and the skin lesions are evident in this picture of the boy illustrated in Fig. 19-5.

The dermatological manifestations of his condition included hypopigmented linear naevi along the dermatomes of the limbs, with whorled, rough and erythematous lesions on the trunk, and scaly, depigmented lesions around the face. Patches of grey hair were present (Fig. 19-7). Hypopigmentation and scaling had occurred until the age of 3 years, followed by an erythematous and photosensitive stage which had shown slow but continued improvement until the time of examination.

Global psychomotor delay was noticed from infancy and his estimated IQ was in the 40-60 range. He had not suffered convulsions and there were no localizing central nervous system signs.

Fig. 19-7: The individual in Fig. 19-5 with linear naevi on the forearm, skin lesions on the trunk, limb asymmetry and greying patches of scalp hair.

The epidermal naevus syndrome is considered the most likely diagnosis in this individual. The manifestations of this disorder comprise a range of congenital naevi which includes the cutaneous changes found in this patient. Skeletal abnormalities (including hemi-atrophy/hemihypertrophy) and neurological complications (including mental retardation) are well recognised concomitants (Solomon et al, 1968).

Two conditions in which developmental neural crest defects are associated with pigmentary disturbance, enter into the differential diagnosis. **Incontinentia pigmenti** comprises dermatological findings similar to those of the Mauritian youth, with associated mental retardation and occasionally, skeletal malformations. However, it is thought to be inherited as an X-linked dominant trait with male lethality (Wiklund and Weston, 1980). **Hypomelanosis of Ito** (Jelinek et al, 1973) is a heterogeneous entity with many features of similarity to the boy described here, although his cutaneous lesions are not characteristic of this disorder (Opitz, personal communication). The discussion of this case highlights the nosological confusion that exists for the disorders of neural crest origin. Until such time as a definitive diagnosis for these conditions is possible, broad categorisation is probably expedient.

The final illustration in this Section concerns the Mauritian boy with the epidermal naevus syndrome and hemi-atrophy. Fig 19-8 was taken on the occasion of his third birthday and affords a unique historical appraisal of his condition; the skeletal malformations are clearly evident and the scaly skin lesions, visible on his limbs and face, appear of similar or even greater severity. In addition, at the time of this photograph, he was being raised as a girl. A deliberate change of gender, for a period of time, is a cultural response in certain communities, to counter the problems that have befallen a child. Genetic disease, physical handicap and the psychosocial repercussions are uniquely captured in this portrait.

Fig. 19-8: The 'boy' with an epidermal naevus syndrome taken during a period of gender transversion, on the occasion of his third birthday.

19.7 CYSTIC FIBROSIS

Cystic fibrosis, one of the most common autosomal recessive genetic diseases deserves mention at this juncture. This entity, which would have been classified in this chapter by virtue of its exocrine gland involvement, is notable by its absence on Mauritius; no case was encountered during the survey. Local practitioners recalled a Franco-Mauritian family with this condition who had emigrated some years previously. As cystic fibrosis has a carrier rate in Caucasians of about 1 in 20 and is also known in India and in the East (McCrae, 1983), the reason for the low gene frequency on Mauritius is a subject for conjecture and further study. It may reflect a negative founder effect amongst the early European settlers or, perhaps, an environmental disadvantage to the heterozygote. Certainly, a tendency for "carrier families", together with their affected children, to emigrate to countries with milder climates and specialised socio-medical facilities, could drastically deplete the cystic fibrosis gene pool on Mauritius. In the absence of continued immigration of gene carriers, it is theoretically possible that this process might have removed the disease from the Island altogether.

SECTION VII

INHERITED DISORDERS ON THE ISLAND OF RODRIGUES

The results of an investigation into inherited disorders on the Island of Rodrigues are presented and discussed in this section. A geographical description of Rodrigues is given and a brief outline of historical events that might have bearing on the pattern of genetic disease on the Island is provided.

CHAPTER 20

THE ISLAND OF RODRIGUES

20.1 INTRODUCTION

The Island of Rodrigues is a socio-politically integrated part of Mauritius. The health and welfare of the Rodriguans falls within Mauritian jurisdiction and this smaller island is included in the planning and establishment of medical services. As both of these islands fall within the same Health authority, a survey of inherited disorders on Rodrigues had practical value and represented a logical extension of the Mauritian study.

Geographically, Rodrigues is clearly separated from Mauritius and this has resulted in a community of independent origins, linked to Mauritius by administrative ties. For the purpose of this thesis, the Rodriguans could thus be regarded as a genetic isolate; the effects of isolation would have the potential to produce a pattern of inherited disorders on Rodrigues that differs significantly from the situation on Mauritius.

In this chapter, the relevant geographical features and historical events that could have bearing on the presence and prevalence of genetic disease on Rodrigues are presented.

Fig. 20-1: The Island of Rodrigues.

20.2 GEOGRAPHICAL FEATURES

Rodrigues lies at a longitude of approximately 63° 25' East and a latitude of 19° 42' South, situated in the Indian Ocean nearly 650 km East of Mauritius (Fig. 3-2). It is 18 km in length and, at its greatest width, measures just over 8 km (Fig. 20-1). The surface area of the Island has never been measured owing to the hilly nature of the land. Indeed, this topographical feature is in direct contrast to the flat cane-lands of Mauritius.

A central ridge divides the Island along its axis. The mountain-sides slope steeply to the shore and are corrugated by a series of ravines. Many areas still remain inaccessible to all but the hardiest of walkers, and travel by road is limited to the major villages (Fig. 20-2).

Fig. 20-2: Rodriguan topography: The coral reef is visible in the distance.

A fringe of coral surrounds Rodrigues and access from the sea is limited to a few breaks in the reef. This barrier prevented the Island from becoming a popular stop-over point for early traders and navigators, and was the cause of numerous ship-wrecks. A number of small uninhabited islands of limestone and volcanic origin lie scattered on the reef.

The climate is mild although the coastal regions become hot and humid in the summer months. Rodrigues lies within the cyclone belt and over 260 cyclones have hit the Island within the past 30 years. Often these winds have a devastating effect with gust speeds measuring up to 225 km per hour.

Frequently, however, the accompanying rain relieves the threat of drought. The Island's isolation, the hilly landscape, the inaccessible valleys and the threat of summer cyclones are all an integral part of the Rodriguan lifestyle.

20.3 THE HISTORY OF RODRIGUES

In the early sixteenth century, an Indian Ocean explorer and traveller, Diogo Rodriguez, discovered the island. Although he never landed, as the coral reef barred easy access, the land was given his name. The Island of Rodrigues was of little interest or importance in the succeeding two centuries, as it lay off the normal trading routes to the East and was devoid of ebony trees. Furthermore, the treacherous coastline provided no natural harbour.

The first attempt at colonisation was by eight Frenchmen who conceived an ideal republic of Protestant refugees, free of Catholic domination. Sent as an advance party, the group landed on Rodrigues on the 1st May, 1691. Life, however, proved dull and monotonous. No ships called, the Protestant colonists never arrived and after two years the absence of women became too hard to bear! The men built a boat and rowed to Mauritius from whence they never returned.

The French government subsequently attempted to establish a colony by sending Catholic families of labourers and artisans from Réunion, all strong and healthy individuals who were accustomed to hard work. Unfortunately, apart from 2 individuals, the 38 inhabitants proved to be men and women of poor moral fibre and remained on the Island no longer than 9 months (North-Coombes, 1971).

During this second attempt at the colonisation of Rodrigues, Leguat (1705) documented 2 zoological phenomena that

illustrate the influence that isolation had had on the fauna of this small Island. Giant tortoises, many over a meter in length and weighing over 50 kilograms, covered the surface of the Island. *("....sometimes you see two or three thousand of them in a flock, so that you may go over a hundred paces on their backs without setting foot to ground.")* In the absence of predators or adverse environmental conditions, these reptiles had had nothing to do but feed, grow and breed for centuries and at the time of Leguat's description they numbered over 200,000. The use of the tortoises on Rodrigues as an ideal source of fresh meat for passing sailors was publicised. The tortoise population was plundered and by the 1760's, almost 10,000 tortoises were removed annually. In 1795, the last 2 animals were discovered in a crevice and eaten.

The Solitaire, a peculiar bird unlike any species previously seen, was described by the early settlers on Rodrigues. The bird weighed approximately 20 kilograms, had a small head, a long neck, residual wings and no tail. The Solitaire was unable to fly, made a loud rattling noise and was friendly and easy to catch. When caged, the bird was said to "shed tears without crying" and would refuse all food until it died. The species, found nowhere else in the world, rapidly became extinct. The natural history of the Solitaire parallels that of the Dodo of Mauritius and amply demonstrates the determining role that a sudden change in environment can have on the survival of a previously viable species.

In 1792, five French families became the first permanent settlers on Rodrigues. Each family unit was provided with a tract of land and lived by farming, fishing and trading. A census was undertaken in 1804 in preparation for an evacuation of the Island pending a British invasion. The results are shown in Table 20-I. These 104 individuals represent a core founder group from whence many of the present day Rodriguans are descended.

HOUSEHOLD	MARRAGON	LEGROS	GORRY	ROCHETAING	BREHINIER	TOTAL
FAMILY MEMBERS	6	1	1	13	1	22
SLAVES :						
MOZAMBIQUE	8	-	9	12	3	32
MADAGASCAR	7	1	5	3	2	18
TALINGA	4	1	-	-	-	5
GUINEA	1	-	-	-	-	1
MALAYSIA	-	1	-	-	-	1
BENGALI	-	1	-	-	-	1
BORN ON RODRIGUES	17	2	5	-	-	24
TOTAL SLAVES:	**37**	**6**	**19**	**15**	**5**	**82**

Table 20-I: The founder individuals of Rodrigues: Results of the census of 1804.

The British occupation of Rodrigues from 1809 until 1812 brought few changes to the Island. The inhabitants continued with their farming pursuits and accepted the influx of 200 British infantrymen and 200 transporters and victuallers. Following the capture of Mauritius in 1812 by the Royal Navy, the British presence on Rodrigues was no longer required and the troops withdrew. However, to quote a Creole expression, "they left a few portraits behind"!

The slaves were freed in 1839, during a period of severe decline on the Island. An attempt to improve conditions on Rodrigues was made from 1843, when magistrates from Mauritius were sent as administrators. Their task proved difficult as the Island was without a prison and there were no churches, shops, schools or facilities for medical care. The census of 1845, recorded 323 Rodriguans: 240 from the original slave population, 83 from the founder "free" population and 1 alien, a shipwrecked Frenchman who elected to stay. The population was broadly divided into those who lived at the coast (the fishermen and the traders) and the cattle farmers and subsistence agriculturists who lived inland (the 'mountaineers'). Interestingly, this broad categorisation exists to this day.

A change of magistrates in 1863 brought an upswing in the development of Rodrigues with the provision of a school, church and prison. The geographical isolation and inhospitable coastline remained major factors in limiting immigration with important effects on the health of the community. Malaria and cholera which had been so devastating

on Mauritius, never reached Rodrigues; plague was undocumented and infectious diseases were very rare. In the absence of a sugar industry, the Island never acquired an indentured Indian labour force and, as there was still no regular transport to Rodrigues, the arrival of settlers (and disease) was a rare event. During the latter half of the 19th century, the only regular input of new people to the Island was from the survivors of an inordinate number of ship-wrecks that occurred off the coastline. By 1880, there were 1400 residents on Rodrigues, with 47 children in school and 47 men in jail.

In 1890, the first streamer arrived on the Island bringing Asian and Chinese traders. Attempts at establishing a tobacco crop were thwarted by the inclement weather and a devastating cyclone in 1903 caused many entrepeneurs to depart. Development languished and by 1950 the provision of education was minimal, there were no newpapers, no radios and no books. Roads were spartan, there was virtually no public transport and church attendance on Sundays was the focal point of the week's activity. Around this time, the establishment of the Eastern Telegraphic Company injected new interest in Rodrigues, with the creation of new work opportunities and subsequent immigration. The regular arrival of a ship from Mauritius, every two months, brought supplies, news and alcohol and became an event of gala proportions.

The population of Rodrigues has expanded rapidly, almost doubling every twenty years despite long periods of isolation. This mercurial growth rate is demonstrated graphically in Fig. 20-3.

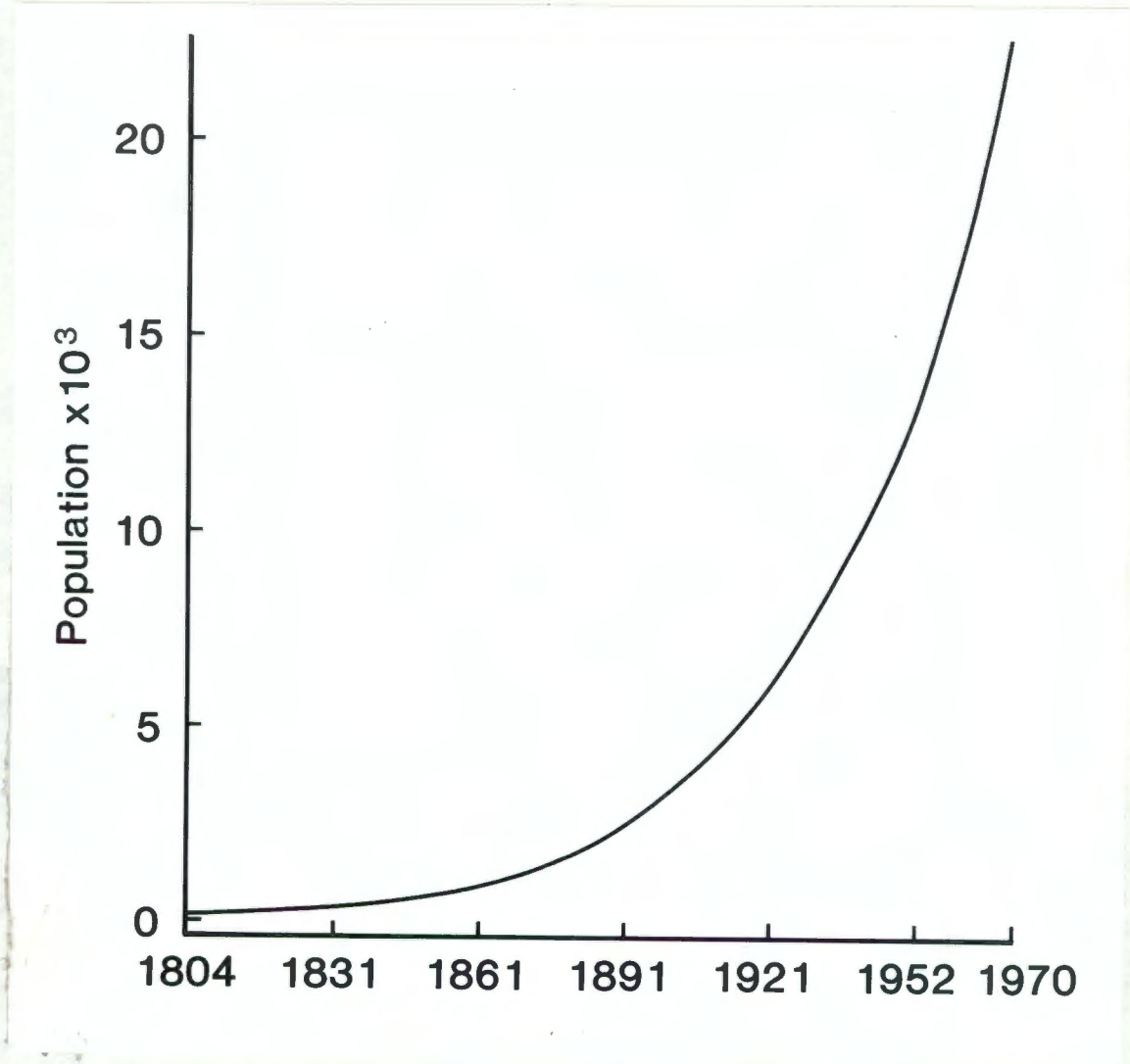

Fig. 20-3: The population growth rate for Rodrigues (1804-1970).

20.4 MODERN-DAY RODRIGUES

Rodrigues is currently governed by Mauritius. The population of approximately 27,000 individuals is almost entirely Creole and many still lead the rural life of subsistence farming and fishing that existed fifty years ago. Transport is limited to a few buses and a small number of private and government-owned vehicles. Modern housing is designed to withstand cyclones and houses lie deep in the valleys and dotted across the hillsides. The predominant religion is Catholicism, the families are large and relatives often remain together within a small geographical area. Crime is rare, the pace is slow and the opportunity for emigration is limited only to the most enterprising. Rodriguans often live to a great age (Fig. 20-4) and the good health of the community is ascribed, in part, to the great distances that are covered on foot in an average Rodriguan life-time!

Fig. 20-4: Five members of the Rodriguan community: Islanders rarely travel without a hat or stick.

Improved communications with the outside world may soon change the character of Rodrigues Island. A runway for aircraft has recently been built and there is regular air-traffic to and from Mauritius. A ship with provisions arrives at six-weekly intervals and passage to Mauritius is now a possibility for many residents. The effects of isolation on the pattern of genetic disease on this small Island may soon be altered or lost. The geographical and historical considerations described in this chapter provide the background to the present study of inherited disorders on Rodrigues.

CHAPTER 21

A SURVEY INTO INHERITED DISORDERS ON RODRIGUES: METHODS, RESULTS AND DISCUSSION

21.1 METHODS

There are no centres for disabled individuals on Rodrigues. For this reason, a survey based on the Mauritian model with the utilisation of specialised institutions as a source of handicapping inherited disorders was not possible.

The health services on the Island comprise a small general hospital staffed by nursing personnel and three medical practitioners, seconded from Mauritius for short terms of duty. The doctors on Rodrigues are essentially outsiders and their awareness of the presence or special prevalence of local genetic disease was inevitably restricted. Notwithstanding, three individuals with genetic disease were referred for assessment by the hospital staff.

A Catholic order of monks is based on Rodrigues. **Les Fréres de St Jean de Dieu,** is represented by three religious brothers who have lived on the Island for the past 15 years. These men work as a community nurse, a social worker and a pharmacist respectively. The pharmacy is a mobile landrover that regularly visits all parts of the Island, including regions without access to public transport. In addition, the monks provide ministry to the Catholic community. Ninety-five percent of the Rodriguan population are members of the Catholic faith, with a church attendance in excess of 90% per

week. In their various rôles, the brothers have earned the respect, co-operation and acquaintance of the Island's residents. They were also aware of individuals with a handicapping disorder and families with more than one similarly disabled member.

Twenty-eight individuals with handicap of a genetic origin were identified and visited in their homes. The investigator had the constant assistance of the *Fréres de St Jean de Dieu* and their secretaries, who were especially skilled in the construction of accurate family pedigrees. The monks' announcements of the survey's aims at all the church services, with a calling for further persons to come forward and be assessed, failed to elicit any additional affected individuals!

21.2 RESULTS

Twenty-eight individuals with genetic disease were examined. The conditions which were diagnosed are listed in Table 21-I.

CONDITION	INHERITANCE	AFFECTED PERSONS
Antecubital pterygium syndrome	AD	5 family members
Undifferentiated deafness	AR	7 cousins
Undifferentiated deafness and night blindness	AR	4 siblings
Alopecia, cataract and sclerodactyly syndrome	AR	3 siblings
Syndactyly	AR	2 sisters
Provisionally private Rodriguan syndrome	AR	2 siblings
Amylo-1,6-glucosidase deficiency	AR	2 individuals
Adams-Oliver syndrome	AR/AD	1 individual
Moebius syndrome	Unknown	1 individual
Trisomy 21	Chromosomal	1 individual

Table 21-I: Inherited disorders documented on the Island of Rodrigues.

21.3 DISCUSSION

Ten different genetic conditions were documented on Rodrigues. The method of ascertainment, although perhaps unorthodox, proved to be effective and efficient in this Island setting.

During the survey, certain conditions manifested with interesting clinical features and some demonstrated important academic or practical points. These examples have been selected for detailed discussion below. Furthermore, two families presented with genetic diseases which are of a special significance to Rodrigues. For this reason, the **autosomal dominant antecubital pterygium syndrome** and the **alopecia, cataract and sclerodactyly syndrome** will be comprehensively documented and discussed in Chapter 22.

21.3.1 Undifferentiated AR Deafness

Two females and five males, all residing in the small Latanier area of Rodrigues, had profound congenital undifferentiated deafness. A genealogical analysis of their families demonstrated two instances of close consanguinity and an autosomal recessive mode of inheritance is proposed (Fig. 21-1). Six of the affected individuals had married unrelated spouses, producing a combined total of 31 children. Each of these offspring is thus an obligatory heterozygous carrier of the deafness gene.

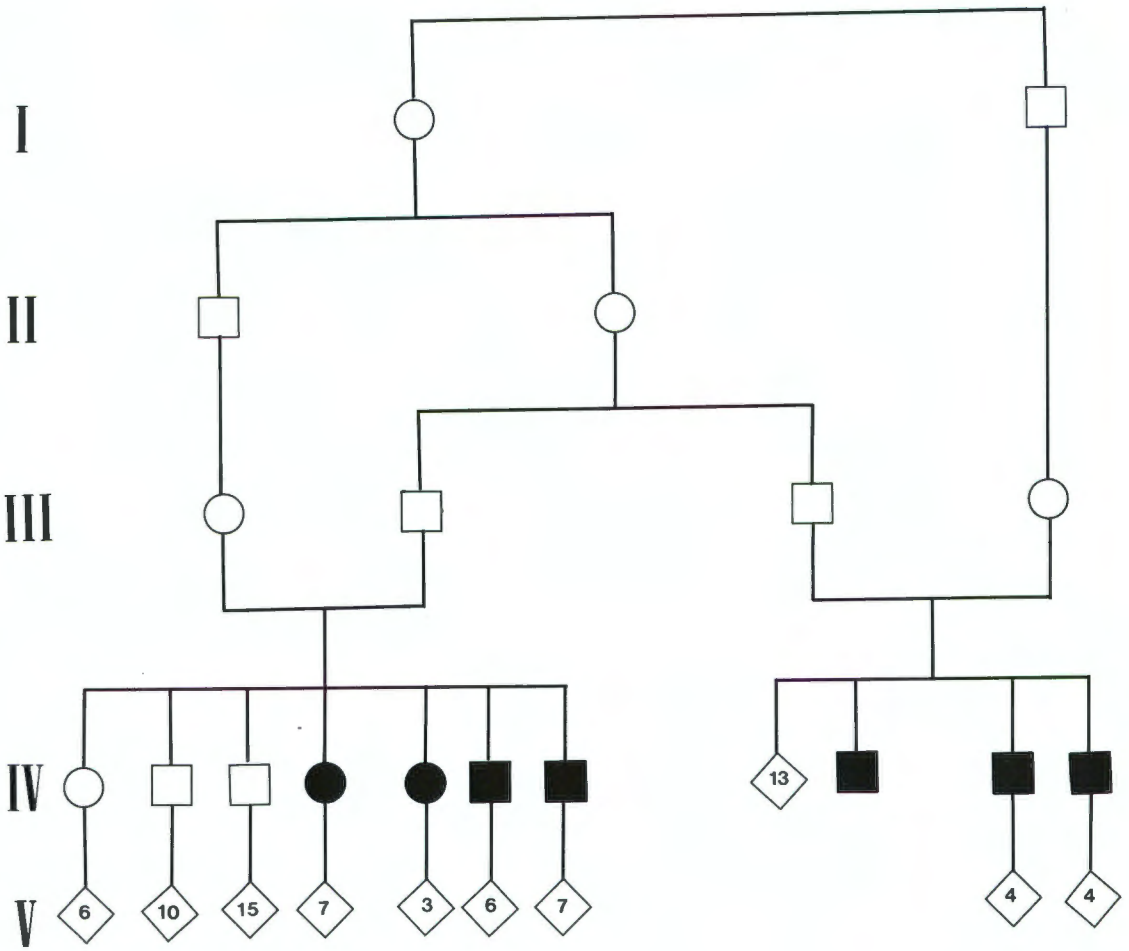

Fig. 21-1: The pedigree of a kindred with undifferentiated AR deafness in the Latanier district of Rodrigues.

Many of the deaf individuals' children have continued to live in the area together with their 27 unaffected cousins, who are themselves at risk of a carrier status. The frequency of heterozygosity for AR deafness in this community, must be exceptionally high. Consanguinity and geographical isolation are both contributing factors and the residents of the Latanier valley were made aware of the risks of deafness in the offspring of future consanguineous marriages.

21.3.2 A Provisionally Private Rodriguan Syndrome

A brother and sister presented with phenotypic features that appear to be unique. A brief case report is presented.

The proband, a girl aged 19 years, was the fifth child of non-consanguineous parents. There was no significant family history and apart from an affected brother, described below, her siblings were entirely normal. Family members are portrayed in Fig. 21-2.

Fig. 21-2: A Rodriguan family, with a previously unreported syndrome, in order of decreasing age: from left to right - the mother of the kindred, a normal son, the proband aged 19, her younger unaffected sister, an affected boy aged 9 years and an unaffected boy aged 3 years.

At birth, following a normal pregnancy and delivery, the proband was found to be blind and had severe ocular abnormalities. Her motor function appeared to develop normally and her intellect, until the age of 8 years, was considered appropriate within the constraints of her visual handicap and social setting. She received no formal education, however, and by the onset of puberty, at age 12 years, she was considered mentally retarded with a progressive regression of mental capacity over the ensuing 7 years. She was consistently shorter in stature than her peers.

On examination, aged 19 years, she was of a proportionately short stature. (Height 135 cm.) She was mentally retarded (IQ approximately 50) and although menstruation was fully established, she demonstrated only small breast development with absent axillary hair and sparse pubic hair. Her ocular abnormalities included micro-ophthalmia and severe microcorneae. The fundi could not be visualised due to the structural eye abnormalities; no cataracts could be detected and vision was limited to light perception. Dysmorphic facial features included a narrow and prominent nasal bridge with distal flaring, a short upper lip and protruding ears. Her hair was thin and sparse and she had a wide alveolar margin with prominent teeth (Fig. 21-3). Systemic examination was normal. There were no obvious skeletal dysplasias or dyshidrosis and her hearing was unaffected.

A brother of the proband, aged 9 years, bore a striking phenotypic resemblance to his sister (Fig 21-4). He was noted to be blind at birth, following an uneventful pregnancy and delivery. His psychomotor development was purportedly normal although he had not received any formal education.

On examination his height was 120 cm (less than 3rd percentile for age), his short stature was proportional and his psychomotor development fell within the lower limits of normality. His hearing was unimpaired and he had no skeletal, visceral or neuromuscular problems.

The ocular changes in this boy resembled those of his older sister (Fig. 21-5) with bilateral micro-ophthalmia and microcorneae. Dysmorphic facial features included cupped ears, a narrow bridge of nose with distal flaring, a wide alveolar margin with protruberant teeth and fine sparse hair.

No facilities for further specialised investigations were available.

Fig. 21-3:

The girl, aged 19 years, demonstrates the ocular changes and facial features of a broad nose, sparse hair and protruberant teeth.

Fig. 21-4:

The similarly affected brother of the proband.

The phenotypic features of micro-ophthalmia, microcornea, sparse thin hair, wide alveolar margins, protruberant teeth, a narrow bridge of nose with distal flare and psychomotor retardation with proportionate short stature apparently constitute a previously unreported ectodermal dysplasia or abnormality of neuroectodermal development. Although consanguinity could not be substantiated, the genealogical information for this family is compatable with an autosomal recessive mode of inheritance.

Utilisation of the Birth Defects Information Computer Service failed to provide an appropriate diagnosis. The Hallermann-Streiff syndrome (Steele and Bass, 1970) shares some of the ocular and ectodermal changes demonstrated by these Rodriguan siblings but the characteristic bird-like facial appearance with a thin and pointed nose is not manifest. It is likely that the disorder described above represents a previously unreported AR syndrome.

21.3.3 Amylo-1,6-glucosidase Deficiency

Consanguineous marriages between two prominent Creole families living along the coastline of Rodrigues have produced an illness in certain of their offspring that is characterised by diarrhoea in early infancy, a swelling of the abodmen and drowsiness that responds to the sucking of sugar cane. Death frequently occurs in infancy or early childhood and is associated with convulsions.

A male infant with these symptoms was fortunate in acquiring a passage to Europe where investigations undertaken at 9 months of age, confirmed amylo-1,6-glucosidase deficiency.

The documentation of this rare AR glycogen storage disease highlights several points of significance to Rodrigues. Although symptomatic in childhood, amylo-1,6-glucosidase deficiency is amenable to dietary therapy and by adulthood, the affected individual may show considerable improvement and virtual recovery (Howell and Williams, 1983). With an accurate diagnosis, appropriate management can be instituted with therapeutic benefit to the patient and family.

An awareness of the presence of this unusual gene in these Rodriguan families could assist in the early clinical detection of future affected neonates. Knowledge of this condition might thus circumvent the need for the special referral of an affected child. Instead, transport of suitable biological specimens for a definitive diagnosis at an overseas centre would become feasible and be of considerable financial and medical advantage.

21.3.4 Adams-Oliver Syndrome

A Rodriguan girl of consanguineous parents, had features compatable with the Adams-Oliver syndrome (Adams and Oliver, 1945). The scalp defect and associated ectrodactyly of the feet are portrayed in Fig. 21-6. Her hands, palate, skull and psychomotor development were all normal.

AD inheritance and variability of expression for this condition is well documented (Hidalgo et al, 1983; Bonafede and Beighton, 1979) and more recently, a newly encountered autosomal recessive form has been suggested (Koiffmann et al, 1988). The description of this Rodriguan girl with the Adams-Oliver syndrome presents further confirmation of heterogeneity for this condition.

Fig. 21-6:
The Adams-Oliver syndrome in a young girl.

21.4 CONCLUDING COMMENTS

A survey of inherited disorders on Rodrigues yielded results which were of academic interest and practical importance. The influence of isolation was evident in the unusual conditions which were encountered.

A study of this nature demands considerably more time and logistical support than is immediately apparent. Large distances have to be covered on foot and time-consuming protocols have to be followed before confidence and trust are gained and a rewarding relationship with the affected individuals can be established. Furthermore, the accurate construction of pedigrees is often complicated by the fact that many Rodriguans share the same family name. These names are not necessarily their own, but were simply given to them by unimaginative magistrates when the need to have a surname was made compulsory by law!

A continuation of this study may well provide still further interesting findings. In particular, the impact of genetic disease on mental retardation warrants further assessment and 2 examples illustrate this point. Access to an isolated valley, where a number of mentally retarded adults were rumoured to live, was barred to the examiner due to local taboos and superstitions. Secondly, trisomy 21 was encountered in only one instance. It is generally accepted by certain sections of this community that the youngest child of a long sibling line may differ in looks and capabilities. Lack of awareness may be a contributing factor for the low

prevalence of trisomy 21. A child with Down syndrome, portrayed in the final illustration of this section, was not considered particularly abnormal by her family and was encountered serendipitously on the roadside. Indeed, she was fully integrated into the special pace of Rodriguan life and quite adequately fulfilled her function within her family: to hang the corn from the bedroom ceiling in safekeeping from the summer's cyclones (Fig. 21-7).

Fig. 21-7: A Rodriguan child with Down Syndrome, seated left in the picture with her mother and a friend, at home, on the bed beneath the corn.

SECTION VIII

GENETIC DISORDERS ON MAURITIUS:

AN OVERVIEW

CHAPTER 22

GENETIC DISEASES OF SPECIAL SIGNIFICANCE TO MAURITIUS AND RODRIGUES

During the current investigation of genetic disorders on Mauritius and Rodrigues, conditions were encountered that proved to be of special academic and practical significance to the community. Four of these disorders are presented separately in this chapter, thus affording to each entity, a more detailed description than would otherwise have been possible. The selection of these conditions was based on their historical importance, their unusual prevalence or their unique phenotypic features.

22.1 HUNTINGTON DISEASE

An unusually high prevalence of Huntington disease in the European population of Mauritius was first documented by Hayden (1979) while investigating the origins of South African families with this condition. In an extension of this study, Hayden et al (1981) were able to link five affected South Africans and 6 affected Mauritians to a common ancestor who emmigrated from France to Mauritius around the year 1800.

During the current survey of inherited disorders on Mauritius, this prime example of the founder effect was reviewed and the 'at risk' relatives and affected individuals on the Island were examined. An updated pedigree of the family (Fig. 22-1) was constructed following interviews with

the descendants, from studies of ancestral diaries and from Hayden's original work. The following discussion refers to this pedigree and emphasizes the influential rôle that history has played on the prevalence of Huntington disease on Mauritius.

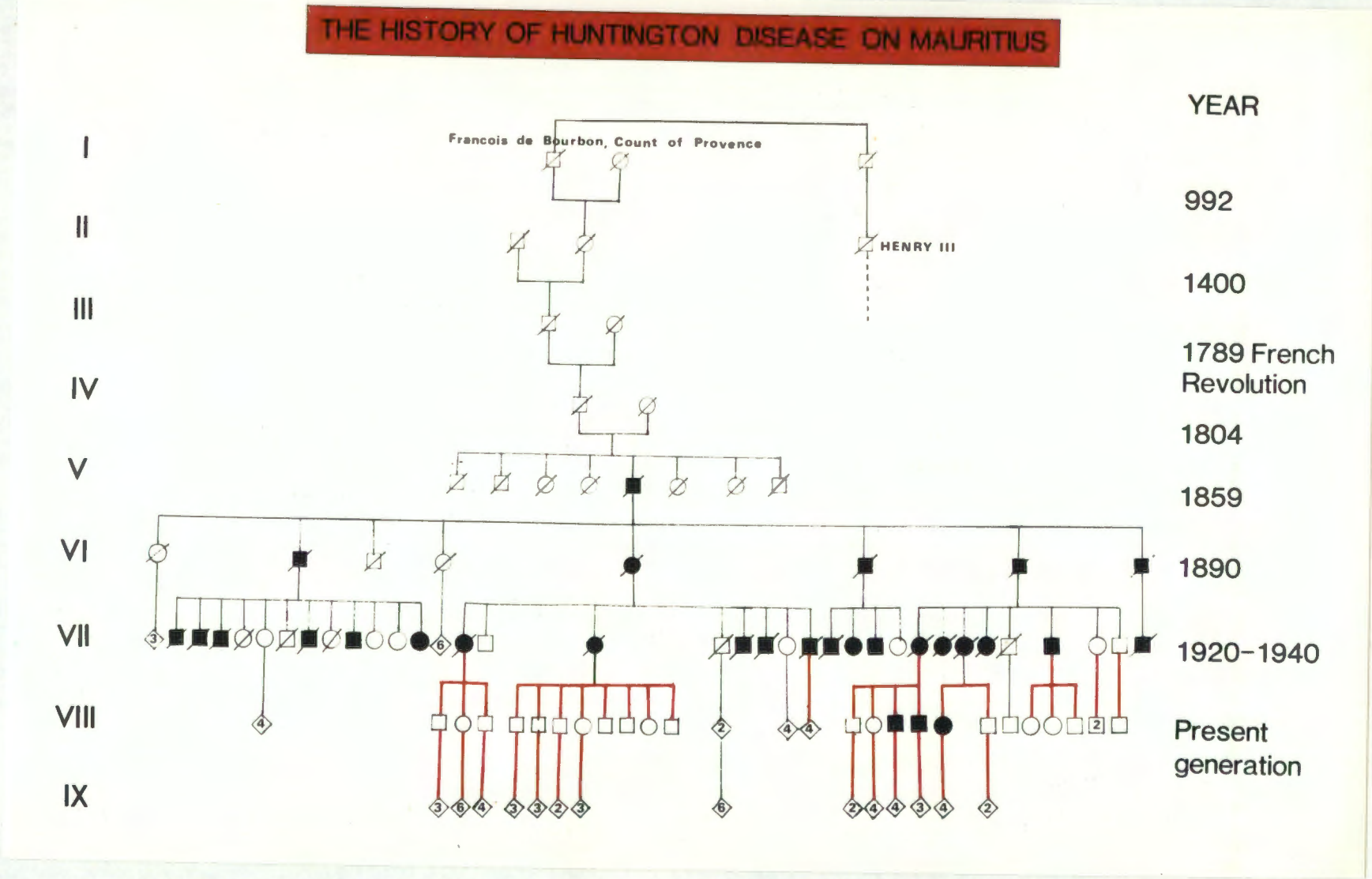

Fig. 22-1: A pedigree of the Bourbon family traces the history of Huntington Disease on Mauritius.

22.1.1 Discussion

Pierre d'Agnel de Assigné de Bourbon (V-5) was the first Mauritian to die from Huntington disease. His father (IV-I) was reputed to have had some abnormal movements but this could not be confirmed. His grandfather, (IV-I), August Benoni Joseph d'Agnel de Assigne de Bourbon was the founder member of this dynasty on Mauritius, having fled France shortly after the revolution in 1789. It is unclear whether he or his wife carried the Huntington gene. Genealogical information concerning this nobleman traces the family back to Francois de Bourbon, Count of Provence in 992 and thus entitles living relatives to include French Royalty amongst their progenitors.

Pierre de Bourbon (V-5), prior to his death in Port Louis in 1915, sired 8 children. Five subsequently died of Huntington disease but not before producing a new generation of 33 children, 20 of whom inherited the abnormal gene. Over three generations the prevalence of Huntington disease on Mauritius thus increased from zero to an estimated 1 in 4000 and equalled amongst the highest rates in the world.

The influence of history once again altered the frequency of this disorder on the Island. Economic depression in the 1940's resulted in the departure of many family members to South Africa, Australia, Réunion and the United Kingdom; emigration is indicated in red vertical lines on the pedigree (Fig. 22-1). One family of 12 siblings, (the progeny of VI-2) remained on Mauritius, each living with the knowledge of a

50% risk for the disorder and therefore the possibility of having affected children. It was for this reason that these remaining brothers and sisters made a pact. They resolved not to procreate and thereby eliminate the Huntington gene from Mauritius. Six of these 12 brothers and sisters subsequently developed the condition; none of the affected persons had married.

A combination of emigration and conscious procreative abstinence has manipulated the prevalence of Huntington disease to negligible levels and dramatically reduced the size of the 'at risk' population. However, a caveat remains for those who believe the presence of this gene has been removed from the Island; there is a twist in this tale of noble conduct.

During the current survey, a middle-aged woman of Hindu extract, the youngest of five children, was examined. She presented with a recent onset of progressive dementia and chorea, for which no cause could be found. There was no relevant family history but the identity of this woman's father could not be definitively ascertained. The clinical picture was compatible with a diagnosis of Huntington disease. She has four teenage children.

22.2 X-LINKED DEAFNESS OF NANCE (XLDN)

X-linked deafness of Nance (XLDN) is a rare but well documented form of mixed progressive deafness with stapes fixation that is characterised by a profuse perilymphatic gusher during attempted stapes surgery (Nance et al, 1971; Thorpe et al, 1974; Cremers et al, 1985). At the time of this survey, XLDN had not been successfully linked to a molecular probe and localization of the abnormal gene was unestablished.

22.2.1 XLDN on Mauritius

A large Hindu family with inherited deafness was encountered on Mauritius. Three generations were available for investigation and the pedigree, shown in Fig. 22-2, was compatible with an XL recessive pattern of inheritance.

The hearing loss in this family was of congenital onset in the affected members and had precluded the development of speech. Examination of the affected males revealed no clinical abnormalities and there was no craniofacial dysmorphism (Fig. 22-3). Audiometric studies had been undertaken on 8 deaf persons. Pure tone air conduction audiometry revealed profound bilateral deafness; bone conduction demonstrated a moderate hearing loss in the lower frequencies. The middle ear pressures were normal on impedence audiometry but a shallow point of maximum compliance indicated possible fixation of the stapes in all the individuals who were tested.

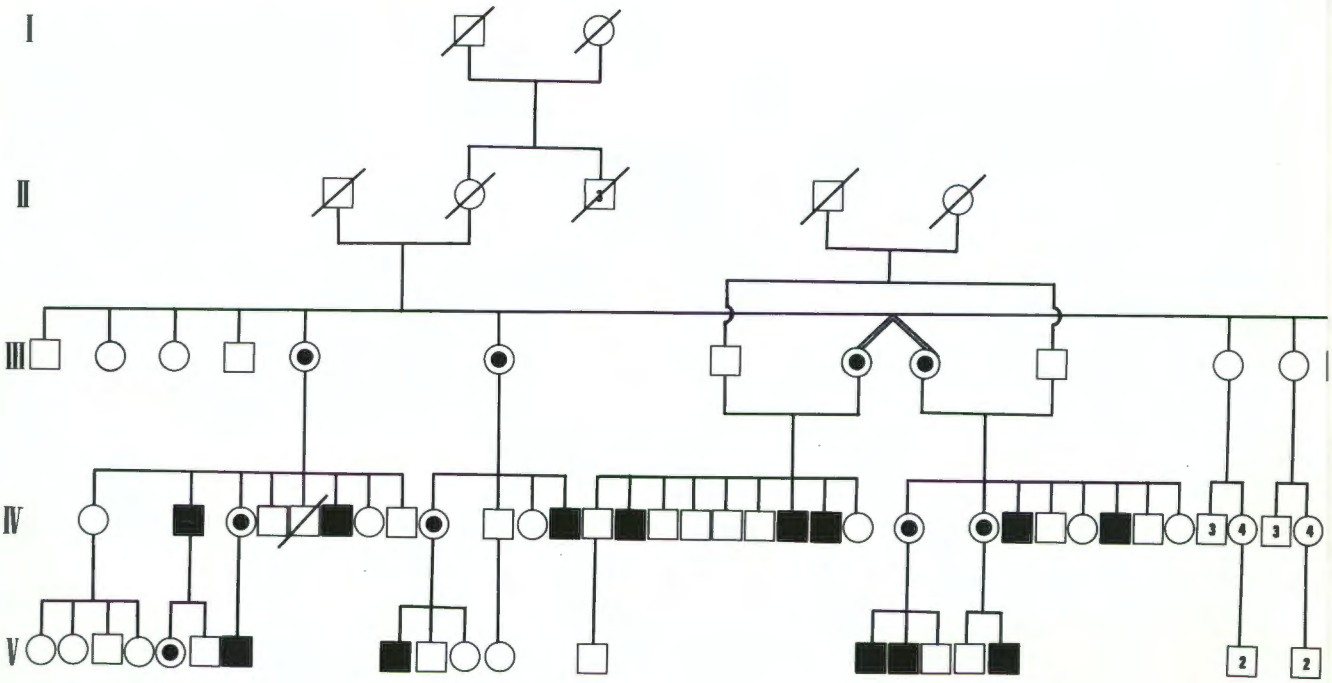

Fig. 22-2: X-linked deafness of Nance: A pedigree of the kindred.

Fig. 22-3: A family with XLDN: The females in this picture are surroundered by their sons, many of whom are deaf.

High resolution cytogenetic studies of peripheral lymphocytes of the affected males at the 600 band level revealed no abnormalities and specifically no microdeletions.

In one individual, a tympanotomy and attempted stapedectomy undertaken 2 years previously, had been complicated by a perilymphatic gusher. On the basis of these findings, the diagnosis of X-linked mixed deafness with stapes fixation and perilymphatic gusher at surgery (XLDN) was confirmed.

All of the carrier females were in good general health, with normal speech and hearing. Audiometric studies of these females were inconsistent and in the case of the four carrier women in generation III (Fig. 22-2) the risks were further complicated by otosclerosis of advancing age. No reliable clinical indicators for the detection of female carriers could be determined.

This family, in terms of affected members, represented the largest kindred yet reported in the literature and presented a unique opportunity for molecular linkage analysis. Not only were there three generations comprising 8 obligatory carrier females, 12 affected males and 11 unaffected males, all living in close proximity to each other (Fig. 22-3), but two of the four founder carrier females (Fig. 22-4) were monozygotic twins and between them had produced 17 offspring. Furthermore, there is currently no reliable procedure for carrier detection (Cremers and Huygen, 1983) and no facility for the antenatal diagnosis of XLDN.

Fig. 22-4: Four sisters in generation III (see pedigree: Fig. 22-2). These women each carry the gene for XLDN.

22.2.2 Linkage Analysis

A sample of 20 ml of EDTA anticoagulated blood was collected from 31 family members and transported to the molecular laboratories at the Department of Human Genetics, University of Cape Town, according to the protocol outlined in Appendix B.

Restriction enzyme digestion, electrophoretic separation and Southern blotting onto nitrocellulose filters was accomplished in accordance with previously reported techniques (Vandenplas et al, 1984). The filters were hybridised with the X-chromosome specific ^{32}P labelled probes pDP34 (DXYS1) and L1.28 (DXS7). pDP34 was chosen because of provisional linkage of the disease to distal Xq probes and

L1.28 was used as a random Xp marker. Linkage analysis was performed with the LIPED programme (Ott, 1974) for the calculation of lod scores at various recombination fractions and the results are shown in Table 22-I.

		LOD SCORES AT VARIOUS RECOMBINATION FRACTIONS								
PROBE	X CHROMOSOME LOCATION	0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4
pDP34	q13-q21.1	6.32	5.85	5.36	4.84	4.28	3.7	3.07	2.4	1.66
L1.28	p11.3		-1.9	-1.1	-0.7	-0.4	-0.3	-0.2	-0.1	-.03

Table 22-I: The results of a linkage analysis for XLDN with the probes pDP34 and L1.28.

No recombinants were obtained in 21 phase known meioses informative for pDP34 and the calculated lod score of 6.32 indicated tight linkage of the gene for XLDN and the probe pDP34.

On the basis of previous reports (Page et al, 1984) concerning the site of this polymorphic locus, the XLDN gene could be localized to the Xq13 -q21.1 region. This finding has important implications for carrier detection and antenatal diagnosis. Investigations of similarly affected kindreds to establish linkage with probes from the Xq13-q21.1 region will, however, be indicated to resolve the issue of heterogeneity and confirm the position of the locus.

The documentation of this Mauritian family highlights the advantages to be gained from studying a rare disorder in a large kindred where familial propinquity is dictated by the island setting.

22.3 AUTOSOMAL DOMINANT ANTECUBITAL PTERYGIUM SYNDROME

More than 3 decades ago a surgeon, now living in retirement on Mauritius, observed a "congenital web formation" of the antecubital fossa in 8 related individuals on the Island of Rodrigues (Shun-Shin, 1954). Contact with this family had been lost over the ensuing years and no subsequent reports of similarly affected families has appeared in the literature.

During the current survey, attempts were made to relocate and re-appraise this unique family. Eventually new generations of the original kindred were traced and four additional affected individuals were recognized. In this way, the natural history of the condition over a forty-year period could be documented, additional manifestations were recognized and AD inheritance was substantiated (Wallis et al, 1988). A description and discussion of the AD antecubital pterygium syndrome on the Island of Rodrigues is presented below.

22.3.1 Clinical Manifestations

All the affected inidivduals were members of an extended family of Creole stock, resident for six generations on Rodrigues. A pedigree of the kindred is shown in Fig. 22-5 and AD inheritance is evident. The founder member on Rodrigues was originally from the neighbouring Island of Madagascar; previous ancestral detail has been lost with the passage of time.

A total of 11 affected family members was documented. They were all of normal intellect and stature and systematic examination revealed no abnormalities other than the soft tissue and musculo-skeletal anomalies in their arms.

The major finding in all affected persons was bilateral antecubital webbing, in which a thick web of tissue stretched from the lower third of the humerus to the upper third of the forearm. The involvement was bilateral and fairly symmetrical in each individual, with the exception of I-I in whom the changes were unilateral (Shun-Shin, 1954). Flexion of the arm against resistance caused a tense contraction of muscles within the web. The long head of triceps was absent although a fibrous cord could be palpated in some of the thinner individuals. Movements at the elbow joints were impaired and although flexion was always full, extension was limited to between 90 and 135 degrees in different individuals. In addition, supination was invariably compromised to some extent. The degree of handicap in the affected persons was in direct proportion to the extent of the webbing. These clinical features are depicted in a composite photograph representing affected individuals from 5 generations (Fig. 22-6).

The skin creases were absent over the dorsal surface of the distal inter-phalangeal joints of the fingers although there was a full range of movement at this site. The digital and palmar creases were otherwise apparently normal.

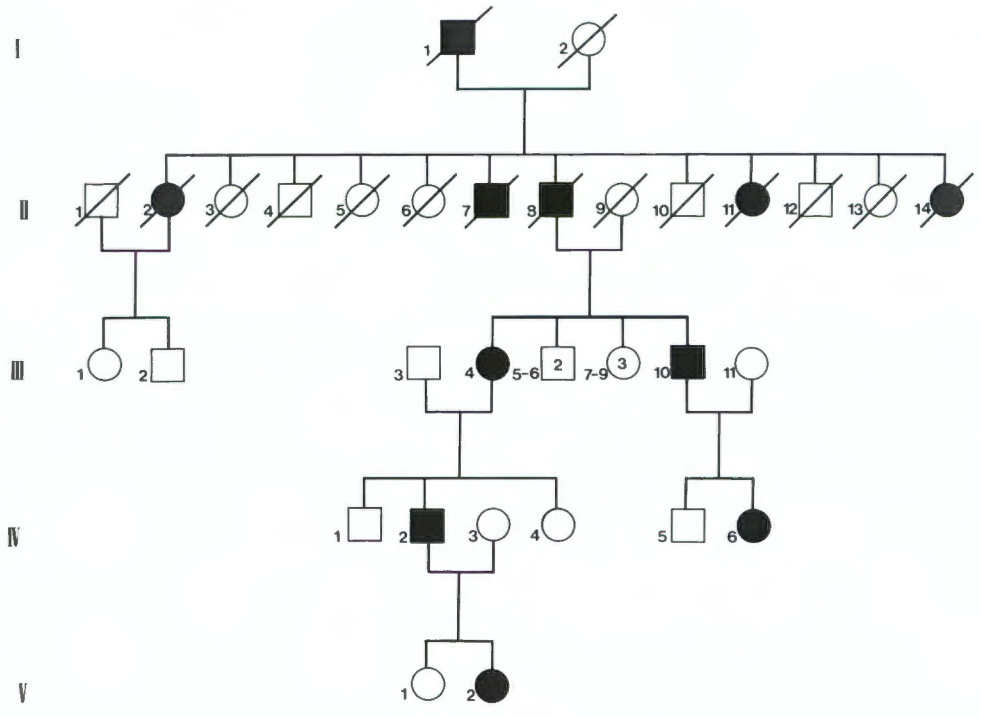

Fig. 22-5: AD antecubital pterygium syndrome: the pedigree.

Fig. 22-6: Five generations with antecubital pterygia: Pedigree numbers correspond to Fig. 22-5.

One individual (III-10) was examined at the age of 10 years in 1947 and again when aged 50 years, during the present survey. Photographs taken on both these occasions are presented in Fig. 22-7. During this 40 year period there had been no significant change in his clinical manifestations and no deterioration in his upper limb function. An attempt at surgical release of the webs during adolescence had had neither beneficial nor detrimental effect.

Radiographic studies of the elbows on one individual revealed bilateral posterior dislocations of the radial heads and hypoplasia of the olecranon processes.

No local practitioners had encountered similar families on Rodrigues or Mauritius during five decades of clinical practice and on this basis the condition appears to be a private syndrome. In view of the affected family's ancestral links with Madagascar, it would be of great interest to learn if the condition is present on that Island.

Fig. 22-7: The AD antecubital pterygium syndrome in a male at age 10 years (left) and age 50 years (right).

22.4 ALOPECIA, CATARACTS AND SCLERODACTYLY SYNDROME

A family with a unique and previously undocumented ectodermal dysplasia was encountered on the Island of Rodrigues. Three affected individuals were studied and a fourth member, who had moved to Mauritius, was examined on a subsequent occasion.

The pedigree of the kindred is depicted in Fig. 22-8 and supports an autosomal recessive mode of inheritance for this disorder. The parents of the 5 affected persons were purportedly unrelated and of Madagascan-Creole, Chinese and Hindu extract. One affected woman (II-2) had produced four normal children; a girl (II-5) with the clinical stigmata of this syndrome had died from gastro-enteritis at age 4 years.

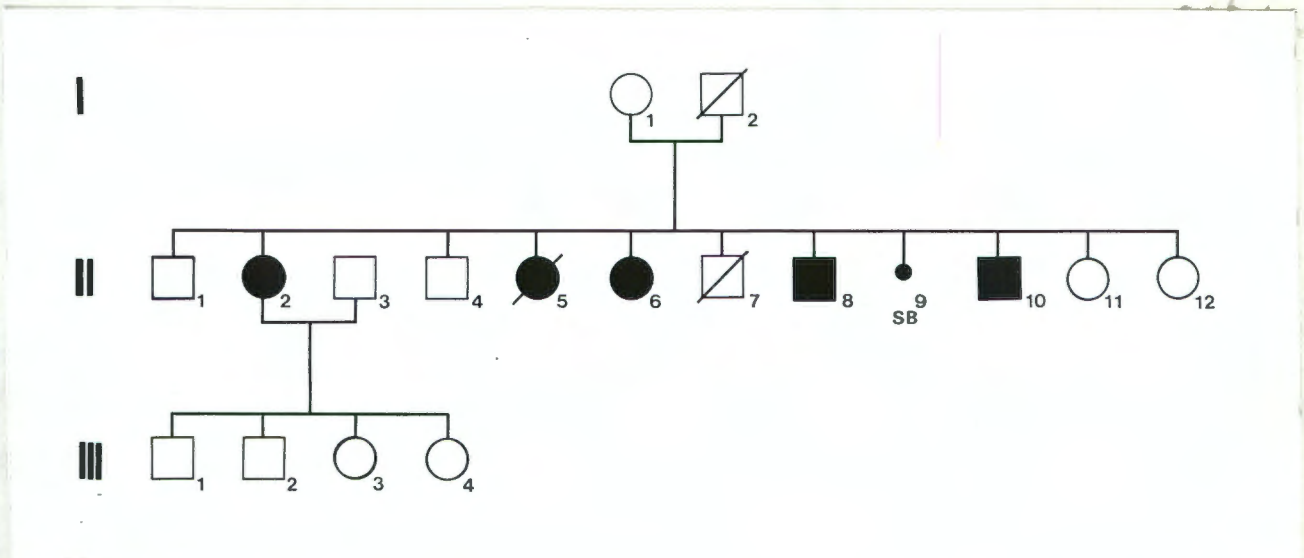

Fig. 22-8: A pedigree of the kindred.

The phenotype for this condition was consistent, fully penetrant and comprised three outstanding clinical features: total alopecia, bilateral cataracts and unusual skin changes to the soles, palms and digits. These clinical findings are depicted in Fig. 22-9. The alopecia was congenital and included all body hair as well as the eyebrows, eyelashes, pubic and axillary hair and beard growth. The cataracts were central and dense and restricted vision to light perception only. The dermatologial changes to the hands and feet appeared to be progressive from birth until late childhood at which stage no further deterioration occurred. The palms and soles were hyperkeratotic with trophic ulcer formation following minor traumatic episodes. The nails were dystrophic and sclerosis with excoriation of the skin of the digits had resulted in deforming bands, nodules and pseudo-ainhum formation. The tips of the fingers were most severely affected and sensation was decreased. There was some secondary limitation to inter-phalangeal movement with contractures of certain joints.

Significant negative findings deserve emphasis. All the affected individuals were of normal intelligence and stature and there were no additional dermatological findings. In particular, there was neither dyspigmentation nor dyshidrosis. There were no abnormalities of dentition and there was no craniofacial or palatal dysmorphology. Systemic examination yielded normal findings, sexual development was complete and a radiographic exmination of the skeleton, including the hands, was unremarkable.

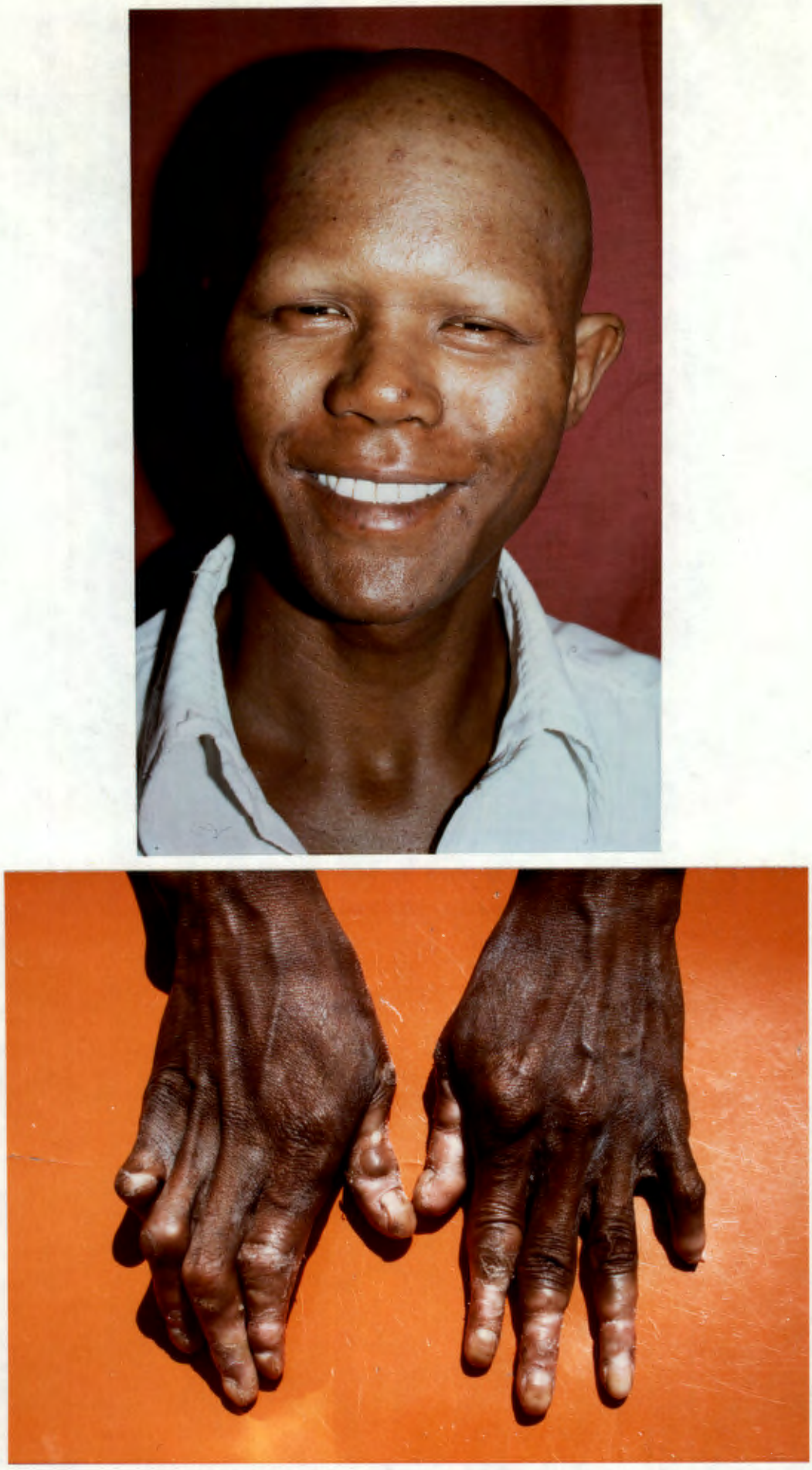

Fig. 22-9: A Rodriguan syndrome with alopecia, cataracts and sclerodactyly with pseudo-ainhum formation.

The chance discovery of two old photographs depicting the three siblings (II-6; II-10; II-8) in Fig. 22-10 is useful in demonstrating the static nature of the phenotype. The skin changes of the hands in Fig. 22-11, at age 14, are unchanged when compared with Fig. 22-9 taken 25 years later.

22.4.1 Discussion

The condition described in this family almost certainly falls within the group of ectodermal dysplasias. The specific combination of features, in the presence of normal dentition, sweating, intellect and stature and the curious skin changes bear no immediate resemblance to any previously described syndrome. The following diagnostic possibilities were entertained and then excluded by the features in parenthesis: **Rothmund-Thomson syndrome** (with generalised skin changes, stunted growth, dysmorphic facies, mental retardation and hypodontia); **Palmoplantar Hyperkeratosis and Alopecia** (probably AD with hyperhidrosis and no evidence of cataracts - Stevanovic, 1959); **Werner syndrome** (with mental retardation and adult progeria) and other sporadic forms of ectodermal dysplasia like **Trichodysplasia-onychogryposis-hypohidrosis-cataract syndrome** (with decreased sweating, brittle hair, mental retardation and short stature - Freire-Maia and Pinheiro, 1984).

It is likely that this family have a hitherto unrecognised syndrome. The genes for this ectodermal dysplasia are present on both Rodrigues and Mauritius following the emigration to the latter Island and subsequent procreation of an affected family member. In view of the AR mode of inheritance, the birth of future affected individuals is

possible. For this reason, the delineation and documentation of this disorder is of value.

Fig. 22-10: Three individuals (II-6; II-10; II-8) portrayed 25 years prior to the current documentation.

Fig. 22-11: The same hands in Fig. 22-9 taken 25 years earlier at age 15 years: little change has occurred.

CHAPTER 23

CONCLUDING COMMENTS

23.1 THE SURVEY

The opportunity to investigate the presence of inherited disorders on an island like Mauritius or Rodrigues is a special privilege. Indeed, the chance to explore and document the pattern of genetic disease in a previously uncharted territory seldom arises. The community under investigation was clearly defined and the origins of the population groups were often known. The genetic implications of the founder effect and inbreeding could be studied and the further division of the Mauritian populus into ethnic subgroups afforded the possibility of a comparative analysis.

Mauritius, albeit a developing country, provided the necessary infrastructure of medical and institutional care to support a survey of this nature. Although clinical assessment and the use of locally available ancilliary services were the mainstay of methodology for this project, sophisticated technology was utilised in selected instances. This need was met by employing the technology and expertise of specialised and established overseas centres of genetic research. The transportation of biological material for investigation proved reliable and logistically feasible. The methods provided a useful model in narrowing the disparity in genetic services that exists between developed and developing communities.

23.2 THE RESULTS

During the project, several of the theoretical advantages of analysing a genetic isolate emerged as practical realities. For instance, conditions with AD inheritance provided several generations of affected individuals all living in close proximity to each other. The island setting minimised geographic dispersal and facilitated a comprehensive documentation and delineation of phenotypes such as **Autosomal Dominant Antecubital Pterygium Syndrome.** In addition, an historical account of a founder member's background was often available and the global dissemination of a dynasty could be traced, as with **Huntington Disease.**

The presence of large families with AR conditions focused attention on unusual entities such as **pyknodysostosis.** Closely consanguineous marriages with many offspring, provided 'new' recessive disorders for study, as in the **Alopecia, Cataract and Sclerodactyly Syndrome** (Wallis et al, 1988). Although such entities may remain 'private syndromes', the experience of McKusick et al (1964) with conditions such as Cartilage Hair Hypoplasia in the Old Order Amish of Pennsylvania, has demonstrated how the phenotype may subsequently be recognized in another unrelated population.

A Mauritian family with **X-linked deafness of Nance,** the largest yet documented in the literature, provided an ideal genealogical structure for analysis at a molecular level (Wallis et al, 1988). Tight linkage of this form of deafness to an X chromosome probe was established; this discovery will be of consequence to similarly affected families in other parts of the world.

23.3 PRACTICAL APPLICATIONS

Mauritius has a rapidly developing medical service. Poliomyelitis, once a common cause of physical handicap, is now unknown, malaria is all but eradicated and the rubella vaccine is now routinely administered. The disease profile for the island is changing and attention, in turn, is being focused on genetic diseases. It was anticipated that, in addition to the academic gain of a thesis, this study might be of practical benefit in this context.

A Mauritian referral centre for patients and families with genetic disease is now under creation. Staffed by specialised medical staff and paramedical auxillaries with an interest in inherited disorders, this service plans to:

- Promptly diagnose and correctly counsel individuals with inherited conditions.
- Detect early complications and ensure proper prophylaxis and appropriate therapy.
- Provide ongoing public education and maintain regular contact with affected families.
- Provide knowledge of local peculiarities in the distribution of genetic disease.
- Maintain contact with established centres of human genetics for specialist advice, the transfer of biological material and the conduction of literature surveys.
- Establish a genetic disease registry.

Considering the geographical setting of Mauritius, a complete ascertainment of genetic disease on the Island is feasible!

23.4 SUMMARY OF THE FINDINGS

The study has documented 681 Mauritians with handicapping disorders, of whom 249 individuals had a well-recognised inherited condition. This information is summarised in Table 23-I. It must be re-emphasized that these are minimum prevalence figures and that acquired causes were not specifically ascertained.

HANDICAP	GENETIC (%)	ACQUIRED (%)	UNCERTAIN AETIOLOGY (%)	TOTAL
Blindness	30 (35,7)	26 (31)	28 (33,3)	84
Deafness	54 (47)	12 (10)	50 (43)	116
Mental handicap	99 (32)	30 (10)	178 (58)	307
Physical handicap	80 (46)	94 (54)	-	174
TOTAL	263 (38,6)	162 (23,8)	256 (37,6)	681

Table 23-I: An aetiological overview of handicapping disorders in 681 Mauritian individuals.

A compendium of inherited diseases which were identified on the Islands of Mauritius and Rodrigues is presented in the final pages of this thesis under the headings:

- Autosomal Dominant Conditions
- Autosomal Recessive Conditions
- X-linked Conditions
- Chromosomal Anomalies
- Genetic Disorders with Unestablished Inheritance Patterns.

The corresponding McK number from McKusick's Catalogue (1986), when available, is indicated. Those conditions which are remarkable by their absence or low prevalence have already been mentioned within the text.

McK. No	CONDITION	TOTAL
10080	Achondroplasia	3
10030	Adams-Oliver syndrome	1
17820	Antecubital pterygium syndrome	5
14790	Articular hypermobility syndrome	4
11420	Camptodactyly	3
16050	Distal myopathy	3
12990	EEC syndrome	5
13002	Ehlers-Danlos syndrome (type III)	2
13510	Fibrous dysplasia ossificans progressiva	1
13676	Frontonasal dysplasia	1
14310	Huntington Disease	3
14600	Hypochondroplasia	1
14890	Klippel-Feil anomaly	1
15790	Moebius syndrome	1
16220	Neurofibromatosis	1
16421	Oculoauriculovertebral dysplasia	3
16620	Osteogenesis imperfecta (Type I)	7
16680	Otosclerosis	6
10160	Pfeiffer syndrome	1
18020	Retinoblastoma	4
18050	Rieger anomaly	1
18590	Syndactyly	5
15450	Treacher Collins syndrome	1
19110	Tuberous sclerosis	2
19350	Waardenburg syndrome	5

Table 23-II: AUTOSOMAL DOMINANT CONDITIONS

McK. No	CONDITION	TOTAL
20310	Albinism	1
20350	Alkaptonuria	1
-	Alopecia, cataracts and sclero-dactyly syndrome	4
21000	Behr syndrome	2
21640	Cockayne syndrome	1
23240	Glycogen storage disease (type III)	1
24250	Ichthyosis	2
24580	Laurence-Moon-Beidl syndrome	1
25360	Limb-girdle muscular dystrophy	2
25260	Mucolipodosis (type III) (probable)	1
26160	Phenylketonuria	1
26240	Pituitary dwarfism	2
25340	Proximal spinal muscular atrophy	3
26580	Pyknodysostosis	2
26860	Rubinstein-Taybi syndrome	1
-	Short stature, micro-ophthalmia and hypotrichosis syndrome	2
27022	Sjögren-Larsson syndrome	1
27730	Spondylocostal dysostosis	1
27280	Tay-Sachs disease	1
-	Undifferentiated familial blindness	16
-	Undifferentiated familial deafness	27
-	Undifferentiated familial mental retardation	32

Table 23-III: AUTOSOMAL RECESSIVE CONDITIONS

McK. No	CONDITION	TOTAL
31010	Becker muscular dystrophy	3
30440	Deafness of Nance	14
31020	Duchenne muscular dystrophy	13
30510	Hypohidrotic ectodermal dysplasia	1
30895	Lesch-Nyhan syndrome	1
-	Undifferentiated blindness	2

Table 23-IV: X-LINKED CONDITIONS

CONDITION	NUMBER
Trisomy 21	65
15p-	1
Turner syndrome	1

Table 23-V: CHROMOSOMAL ANOMALIES

CONDITION	NUMBER
Enchondromatosis with dwarfism and deafness	1
Epidermal naevus syndrome	1
Familial hydrocephalus	2
Familial mental retardation	2
Hypohidrotic ectodermal dysplasia	2
Mental retardation and marfanoid habitus	3
Moebius syndrome	1
Oculoauriculovertebral dysplasia	3
Osteogenesis imperfecta	2
Retinitis pigmentosa	2
Spino-cerebellar ataxia	1
Unclassifiable muscular dystrophy	2

Table 23-VI: GENETIC DISORDERS WITH UNESTABLISHED INHERITANCE PATTERNS

SECTION IX

APPENDIX

AND

REFERENCES

APPENDIX A

DEPARTMENT OF HUMAN GENETICS OCEANIC ISLAND GENETIC SURVEY

1. DATE ____ ____ ____

2. SURNAME _____

3. CHRISTIAN NAME _____

4. DATE OF BIRTH ____ ____ ____ 5. AGE ____ 6. SEX ____

7. HOME ADDRESS _____

_____

8. PLACE OF BIRTH _____

9. REFERRAL CENTRE _____

_____

10. GROUP DIAGNOSIS i) _____

ii) _____

11. ETHNIC GROUP _____

_____

12. PEDIGREE 13. CONSANGUINITY: YES/NO

GESTATION: 14. WEEKS _____ 15. ILLNESS _____ 16. DRUGS _____

BIRTH: 17. MODE _____ 18. WEIGHT _____

19. PROBLEMS _____

20. SMILED _____ 21. SAT _____ 22. WALKED _____ 23. TALKED _____

24. MEDICAL HISTORY

EXAMINATION

25. WEIGHT _____ 26. HEIGHT _____ 27. COH _____ 28. SPAN _____

HEAD: 29. SHAPE _____ 30. FONTANELLE _____

FACE 31. EARS: _____ 32. NOSE _____

EYES: 33. SIZE _____ 34. EPICANTHIC FOLDS _____

35. HYPER/HYPOTELORISM _____

36. FUNDI _____

MOUTH: 37. SHAPE _____

38. LIPS _____ 39. PALATE _____

40. GUMS _____ 41. OTHER _____

42. CHIN _____ 43. MALAR REGION _____

UPPER LIMBS 44. ARMS _____ 45. JOINTS _____

46. FINGERS _____ 47. NAILS _____

48. PALMS _____ 49. CREASES _____

LOWER LIMBS 50. LEGS _____ 51. JOINTS _____

52. TOES _____ 53. NAILS _____

54. SOLES _____

55. SKIN _____

56. HAIR _____

57. THORAX & SPINE _____

58. ABDOMEN _____

59. PELVIS & HIPS _____

60. GENITALIA _____

NEUROLOGY: 61. TONE _____

62. INTELLIGENCE _____

63. VISION _____

64. HEARING _____

65. FINAL ASSESSMENT

66. PHOTOGRAPHS ___ to ___ 67. X-RAYS ___ 68. BLOODS ___ 69. CONSENT ___

APPENDIX B

Transportation of biological specimens from Mauritius to an overseas centre.

1. Blood for chromosome analysis: A good culture can be grown with:
   i) 2 ml of whole blood in lithium heparin.
   ii) At room temperature if transit time is 12-18 hours.
   iii) At 4 degrees centigrade if transit time is greater than 18 hours.
   iv) Do not freeze.

2. Blood for DNA linkage analysis: A good yield can be achieved with:
   i) 30 ml of whole blood in EDTA.
   ii) At room temperature if transit time is 8 hours.
   iii) At 4 degrees centigrade if transit time is up to 48 hours.
   iv) Do not freeze.

3. Skin biopsies for analysis:
   i) Using sterile forceps place skin in sterile container.
   ii) The transport medium may consist of saline, or the patients own heparinised blood taken under sterile techniques.
   iii) Store at 4 degrees centigrade for all transit times.
   iv) Do not freeze.

APPENDIX C

Lymphocytes were cultured for 72 hours in 199 tissue culture medium and phytohaemagglutinin but without the addition of fetal calf serum.

One hundred cells were counted routinely and any metaphase plate with a fragile site was destained and G-banded to identify whether the X chromosome was involved.

In addition 10 banded metaphases were screened to detect additional chromosomal aberrations.

APPENDIX D

HANDICAP MENTAL OU PHYSIQUE

Un médecin sud-africain étudie les maladies génétiques à Maurice

LE Dr Colin Wallis, qui est affecté au département du *"Human Genetics"* à Cape Town, Afrique du Sud, effectue actuellement une étude à Maurice dans le but de connaître le rôle précis que jouent les maladies génétiques chez les personnes souffrant d'un quelconque handicap, que ce soit mental ou physique.

Cette étude a démarré depuis le début de mars dernier. Elle prendra fin dans environ deux semaines. Le rapport final ne sera soumis qu'après une année.

UNE NÉCESSITÉ

Pour le Dr Wallis, une telle étude est devenue une nécessité à l'île Maurice du fait que ce pays a fait des progrès immenses en ce qui concerne le programme de santé primaire. Le département de *"Human Genetics"* de l'Université de Cape Town a déjà effectué une étude semblable au Zimbabwe.

RENCONTRES

Dans le cadre de cette enquête, le Dr C. Wallis rencontre actuellement des familles ayant des enfants qui souffrent d'un handicap quelconque. Pendant les deux semaines qui suivent, ces familles pourront le contacter en téléphonant au 6-4400.

MIEUX CONNAÎTRE LA SITUATION MAURICIENNE

Un des objectifs de cette étude permettra de mieux connaître la situation mauricienne en ce qui concerne les maladies génétiques. A partir de là, les médecins mauriciens vont pouvoir trouver un terrain confortable leur permettant de donner des conseils nécessaires aux familles concernées.

UN DÉFI

Pour le Dr Wallis, la possibilité de déplacer les gènes responsables d'une défectuosité chez un être humain est un défi que vont devoir relever les générations de scientifiques futures.

LIEN DE PARENTÉ

Selon le Dr Wallis, une des causes de maladies génétiques, maladies qui sont transmises aux enfants par leurs parents, serait la réunion de couples qui ont un lien de parenté très proche entre eux. Des mères affectées directement, a indiqué le Dr Wallis, peuvent transmettre certaines maladies génétiques, dont la dystrophie musculaire à leur fils.

SENSIBILISATION DES PARENTS

Le Dr Wallis a mis l'accent sur l'éducation et la sensibilisation de parents à repérer la présence de maladies génétiques chez leurs enfants. L'expérience qu'il a eue a démontré qu'après que des parents ont compris que personne n'est responsable de l'état actuel de leurs enfants atteints de maladies génétiques, ils sont plus aptes à les aider à développer au maximum les potentiels dont ils disposent.

A L'HEURE DU MARIAGE

Le médecin de Cape Town s'est gardé de tracer une ligne de conduite dans le domaine du mariage. Car, fait-il remarquer, ce sont les personnes concernées qui doivent prendre la décision finale. Toutefois, a-t-il ajouté, les informations concernant les origines des maladies génétiques doivent circuler de manière à permetre à la population d'être avisée des risques réels que comporte, parfois, l'union de couples provenant d'une souche de parenté très proche.

APPENDIX E :

Year of census	Indo-Mauritian population			Chinese population		
	Both sexes	Male	Female	Both sexes	Male	Female
1846	56,245	48,935	7,310	-	26	-
1851	77,996	64,282	13,714	-	-	-
1861	192,634	141,615	51,019	1,552	1,550	2
1871	216,258	141,804	74,454	2,287	2,284	3
1881	248,993	151,352	97,641	3,558	3,549	9
1891	255,920	147,499	108,421	3,151	3,142	9
1901	259,086	143,100	115,986	3,515	3,457	58
1911	257,697	138,974	118,723	3,662	3,313	349
1921	265,524	139,150	126,374	6,745	5,233	1,512
1931	268,649	139,533	129,116	8,923	6,343	2,580
1944	265,247	136,382	128,865	10,882	6,808	4,074
1952	335,327	171,241	164,086	17,850	10,421	7,429
1962	454,909	230,669	224,240	23,058	12,654	10,404
1972	565,248	284,443	280,805	24,084	12,849	11,235

Comparative Growth of Indo-Mauritian and Chinese Communities 1846 - 1972.

APPENDIX F

Routine screening of DNA from the affected males failed to detect a deletion of the X chromosome using the X-linked probes: pERT 87 (subclones 1, 8 and 15) and the XJ series (1,1 and 1,2).

It is anticipated that probing with the recently acquired cDNA clones will detect the presence of smaller deletions within this area. Regretably, the results of these investigations were not available in time for submission of this thesis.

In the absence of a deletion, linkage studies will be undertaken on this family using intragenic probes and flanking markers.

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